Title (en)

MUTEINS OF INTERLEUKIN 4 SHOWING LOW-AFFINITY AND SHORT-TERM INTERACTION WITH THE COMMON $g(g) CHAIN

Title (de)

INTERLEUKIN-4 MUTEINE MIT NIEDRIGEN AFFINITÄT UND EINER KURZZEIT-WECHSELWIRKUNG MIT DER GAMMA C-KETTE

Title (fr)

MUTEINES D'INTERLEUKINE 4 PRESENTANT UNE INTERACTION A FAIBLE AFFINITE ET A COURT TERME AVEC LA CHAINE $g(g) COMMUNE

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Application

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Abstract (en)

[origin: EP0911401A1] Human IL-4 (IL-4), one of the small 4-helix-bundle cytokines, uses the specific IL-4 receptor a chain together with a promiscuous subunit, the common gamma chain (gamma c) for transmembrane signaling. The ligand-binding properties of gamma c, which are presently poorly understood, were analysed by biosensor techniques employing recombinant ectodomains gamex (gamma c) and IL4-BP (a) of the receptor chains. The formation and decay of a ternary complex between solute gamex and IL-4 liganded IL4-BP could be established to exhibit a low affinity (Kd = 3 mu M) as well as a short half life t1/2 = 7s. This binding affinity resulted to the major part from the interaction of gamex with IL-4 and not from a direct contact of IL4-BP and gamex, since the binary complex between solute gamex and immobilized IL-4 showed an only 50fold greater Kd of 150 mu M. The IL-4 residues involved in gamex binding were identified by means of an alanine-scanning mutational approach. A functional gamex binding IL-4 epitope is proposed comprising I11, N15, and Y124 as major determinants. Even IL-4 variants which bind gamex 300fold weaker than IL-4 with a dissociation half life t1/2 of less than 1s, retained a substantial T-cell proliferative activity. These findings suggest that low affinity gamma c binding and short half lives of the heterodimeric a/ gamma c receptor complex are sufficient for initiating IL-4 dependent signal transduction.

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