Targeting the IL-15 Receptor with an Antagonist IL-15/Fc γ 2a Protein Blocks DTH and Enhances the Acceptance of Islet Allografts

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Owing to shared receptor components, the biological activities of IL-15 are similar to those of IL-2. However the patterns of tissue expression of IL-2/IL-2R α and IL-15/IL-15R α differ. The development of agents targeting the receptor and signaling elements of IL-15 may provide a new perspective for treatment of disease associated with expression of IL-15/IL-15R. We designed, genetically constructed and expressed a receptor specific IL-15 antagonist by mutating glutamine residues within the C-terminus of IL-15 to aspartic acid and linked this mutant IL-15 to murine Fc γ 2a. These IL-15 mutant/Fc γ 2a proteins specifically bound to the IL-15R, competitively inhibited IL-15 triggered cell proliferation and did not activate the Jak-STAT signaling pathway. We examined the immunosuppressive activity of this agent because of prolonged half-life and the potential for destruction of IL-15R+ leukocytes. The IL-15 mutant/Fc γ 2a fusion proteins markedly attenuated antigen specific DTH responses in Balb-c mice comparing with the responses in the mice treated with control IgG and decrease cellular infiltration within the DTH sites. Intraperitoneal injection of this mutant protein enhanced the acceptance of crude islet allografts from DBA/2J (H-2d) to B6AF1 (H-2b/d, k) rendered diabetic by injection of streptozotocin (15 vs >65 days). These findings suggest that i) IL-15/IL-15R+ cells are crucial to cell mediated immune responses in vivo, and ii) IL-15 mutant/Fc protein may have therapeutic potential in treating diseases caused by cell mediated immune responses.