The multisubunit interleukin-2 receptor : a target for immunotherapy

Thomas A. Waldmann, M.D.

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There are three forms of cellular receptors for IL-2 : one with a very high, one with an intermediate, and one with a lower affinity. We proposed a multichain model for the high affinity IL-2 R involving two IL-2 binding proteins : a 70/75 kDa IL-2 R β and a 55 kDa IL-2 R α (Tac) protein. A series of additional proteins including Class I HLA molecules, ICAM-1, a tyrosine kinase as well as proteins of 22, 30-45, 75 (non-IL-2 binding), and 95-105 kDa have been associated with the two IL-2 binding proteins. In contrast to resting normal T cells that do not express high affinity IL-2 receptors, the abnormal T cells of patients with select autoimmune disorders, individuals rejecting allografts, and patients with certain forms of leukemia/lymphoma express the IL-2 R α protein. To exploit this difference in IL-2 receptor expression, different forms of IL-2 receptor directed therapy have been initiated including (a) unmodified antibody (anti-Tac) to the IL-2 R α receptor, (b) IL-2 truncated

toxin fusion proteins (e.g., IL-2 PE 40), (c) a single chain antibody toxin fusion protein [anti-Tac (Fv)-FE 40], (d) isotopic (e.g., ^{90}Y or ^{212}Bi chelates of anti-Tac), (e) "humanized" anti-Tac with the mouse anti-Tac light and heavy chain complementarity determining regions joined to human kappa light chain and IgG₁ human heavy chain framework and constant regions. The "humanized" hyperchimeric anti-Tac molecules manifested improved pharmacokinetics, reduced immunogenicity, and a new activity of ADCC with human mononuclear cells that was absent in the parental mouse anti-Tac. Thus our present understanding of the IL-2/IL-2 R system opens the possibility for more specific immune intervention strategies. The clinical application of IL-2 receptor directed therapy represent a new perspective for the treatment of certain neoplastic diseases, autoimmune disorders, graft versus host disease, and for the prevention of allograft rejection.