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The Effects of IL-10/Fc Fusion Protein on Long Term Allograft Survival

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〈요 약〉

IL-10 originally termed cytokine synthesis inhibitory factor has anti-inflammatory and suppressive effects on most haematopoeitic cells and is involved in induction of peripheral tolerance via its effects on T-cell-mediated responses. However, IL-10 also functions as a cytotoxic T cell differentiation factor, which promotes a higher number of cytotoxic T cell precursors to proliferate and differentiate into effector cytotoxic T cells. In addition, the effect of IL-10 on organ transplantation has shown a contrast outcome according to factors including timing, kinetics, and amounts of cytokines, as well as the relative impact of the different activities of IL-10 in each particular experimental scheme and model system. Previously our group observed that administration of non-lytic IL-10/Fc fusion protein, a long-lasting form of IL-10, accelerated islet allograft rejection in mice. Thus, a defined role for IL-10 in transplantation tolerance remains controversial, perhaps reflecting both the immunostimulating and immunosuppressive properties of this cytokine. Since rapamycin, a new immunosuppressive agent, is able to inhibit CD4 and, more profoundly, CD8 T cells proliferation and expansion in response to alloantigen in vivo, we hypothesized that IL-10/Fc fusion protein would synergize with rapamycin to promote allograft tolerance. In an in vivo proliferation assay in which CFSE-labeled splenocytes from C57 BL/6 mice were adoptively transferred into MHC fully mismatched, irradiated DBA/2 mice, both IL-10 and rapamycin inhibited both CD4 and CD8 T cell proliferation. However, the combined therapy inhibited them much more than individual therapy. This hypothesis was also tested in an islet allograft model in which DBA/2 islets were transplanted into C57 BL/6 mice rendered diabetic by streptozotocin. Treatment with IL-10/Fc fusion protein alone could not prolong graft survival (MST; 10 days, n=8). However, treatment with rapamycin by five doses prolonged islet grafts survival in 33% of recipients (4/12). In contrast, combined treatment with IL-10/Fc fusion protein and rapamycin produced indefinite islet allograft survival in most cases (16/17). Collectively, despite its anti-inflammatory and immune suppressive effects, IL-10 treatment alone could not prolong the allograft survival. However, IL-10/Fc is synergetic with rapamycin to induce long term allograft survival.