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Copolymer 1 inhibits immune rejection

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Transplantation procedures have become an important and effective therapy for many life threatening diseases, by both bone marrow reconstitutions and organ transplantations. However, immune injection is still the major barrier to successful transplantations. This is manifested in graft versus host disease (GVH) in case of bone marrow transplantations, as well as in functional deterioration and graft rejection in case of organ transplantation (host versus graft - HVG). Current strategies for prevention of immune rejections rely on the use of non-specific immunosuppressive drugs, which induce severe toxic side effects and render patients vulnerable to infections. Thus, in spite of extensive efforts, transplantations have limited success as a therapeutic approach for long term survival. The pathological process of immune rejection is mediated by T-cells, that recognize alloantigens, presented on self major histocompatibility complex (MHC) molecules as non-self. They then proliferate, secrete cytokines and recruit additional inflammatory and cytotoxic cells. In order to prevent immune rejection it is therefore essential to inhibit alloantigen presentation and inflammatory cytokine secretion.

The immunomodulator Copolymer 1 (Cop1, GLAT) which is currently used to treat multiple sclerosis, is well tolerated with only minor side reactions. A unique feature of Cop1 is its promiscuous binding with high affinity to various class II MHC molecules from mouse and human origin, which can lead even to displacement of antigens that are already bound to the MHC groove. In addition, Cop1 is a potent inducer of regulatory T cells of the Th2 type that secrete high amounts of anti-inflammatory cytokines. In view of this cumulative data we attempted to find out whether Cop1 can suppress the pathological process of immune rejection.

Using the B10D2 into BALB/c model of lethal GVH, which is similar to the MHC matched bone marrow transplantation in human, we demonstrated that Cop1 prevents GVH disease. Thus, post transplantation administration of Cop1 over a limited time significantly reduced the incidence, onset and severity of the disease, resulting in improved long-term survival. Cop1 treatment completely abolished cytotoxic activity towards host targets, prevented the pro-GVH IL-2 and IFN-γ cytokine secretion, and induced beneficial Th2 anti-inflammatory response.

We than tested whether Cop1 can also inhibit graft rejection, which presents a more prevalent problem in human transplantation. The effect of Cop1 on graft rejection was tested in two transplantation systems: skin and thyroid grafting assays. It was found that daily administration of Cop1 inhibited graft rejection in both systems. The beneficial effect of Cop1 was manifested in the survival as well as in the retention of function of the transplanted grafts as demonstrated by the postponement of the vigorous process of skin rejection and the increased iodine absorbance of the transplanted thyroid tissue. Cop1 prolonged skin graft survival and inhibited functional deterioration of thyroid grafts in various strain combinations, across minor and major histocompatibility barriers, more efficiently than Cyclosporin, and its effect was comparable to that of the potent immunosuppressive drug FK506.

As for the mechanism of Cop1 activity on graft rejection, it was found that Cop1 interferes with host reactivity towards the graft, as demonstrated by its ability to inhibit the proliferation, IL-2 and IFN-γ secretion of graft specific T cell lines, when incubated in vitro with the stimulating allogeneic cells. Moreover, spleen and lymph node cells from Cop1 treated mice, as well as the T cell lines generated from them, demonstrated a pronounced inhibition of proliferation and Th1 cytokine secretion in response to graft cells. In addition, cells from Cop1 treated mice secreted high amounts of Th2 cytokines (IL-4, IL-5, IL-6, IL-10 and TGF-β) in response to Cop1, and small but significant amounts of Th2 cytokines, mainly IL-10, in response to allograft cells. Thus, Cop1 treatment inhibited the Th1 response to the graft and induced a Th2 cytokine secretion in response to both Cop1 and graft cells, leading to prolonged survival and improved function of the transplanted grafts.

These findings suggest that Cop1 can be a candidate drug for prevention and treatment of immune rejection resulting after organ as well as bone marrow transplantation. The use of Cop1, which is very well tolerated and does not induce general immune suppression, may pave a new way for effective transplantations.

Selected Publications

Aharoni, R., Schlegel PG., Teitelbaum, D., Roikhel-Karpov, O., Chen, Y., Arnon, R., Sela, M. and Chao, N.J. (1997). Studies on the mechanism and specificity of the effect of the synthetic random copolymer GLAT on graft-versus-host disease. Immunol. Lett. 58, 79-87.

Aharoni, R., Teitelbaum, D., Arnon, R., and Sela, M. (2001) Copolymer 1 inhibits manifestations of graft rejection. Transplantation 27, 613-620.