Hugo Rädler
Dr. med

COMPLEMENT REGULATION OF T-CELL ALLOIMMUNITY

Fach: Immunologie
Doktorvater: Prof. Dr. med G. Opelz

Whereas the complement system was originally discovered as a serum component that 'complemented' antibodies in the killing of bacteria, it is now apparent that complement has a multitude of other functions. Understanding complexities of complement's contributions to transplant injury requires an understanding of the various activation pathways, as well as comprehension of the expression and function of complement regulatory proteins and the source of the complement (serum or non-liver-derived). Emerging data indicate that immune cell-derived complement activation physiologically regulates immune cell survival and proliferation, modulating the strength and phenotype of adaptive T cell immune responses involved in alloimmune transplant rejection.
CD8 T cells primed by transplantation recognize allogeneic class I MHC molecules expressed on graft vascular endothelium and contribute to allograft injury.
In the experiments shown herein the impact of local complement production/activation on T cell/endothelial cell (EC) interactions was tested. Proinflammatory cytokines were found to upregulate alternative pathway complement production by ECs, yielding C5a. ECs deficient in the cell surface C3/C5 convertase regulator decay accelerating factor (DAF, CD55) induced greater CD8 T cell proliferation and more IFNγ+ and perforin+ effector cells than wild type (WT) ECs. Allogeneic C3−/− ECs induced little or no CD8 responses. Abrogation of responses following C5a receptor (C5aR) blockade, or augmentation following addition of recombinant C5a demonstrated, that the effects were mediated through T cell-expressed-C5aR interactions. Analyses of in vivo CD8 cell responses to transplanted heart grafts deficient in EC DAF showed similar augmentation. The findings reveal that EC-derived complement triggers secondary CD8 T cell differentiation and expansion.
In sum, the data show that productive CD8 T cell/EC interactions are dependent upon EC-produced and locally activated complement. In addition to explaining the requirement of cytokines as activators of ECs, the data support the concept that therapies targeting complement/complement receptors may be effective in treating autoimmunity and transplant rejection where cognate T cell/EC interactions contribute to tissue injury.
Considering the increasing evidence that, besides mediating antibody-initiated vascular allograft injury, complement also functions as a modulator of alloreactive T cells, it was tested whether blockade of complement activation at the C5 convertase step affects T cell-mediated cardiac allograft rejection in mice. The anti-C5 mAb BB5.1, which prevents the formation of C5a and C5b, synergized with sub-therapeutic doses of CTLA4Ig to significantly prolong the survival of C57BL/6 heart grafts that were transplanted into naive Balb/c recipients. Anti-C5 mAb treatment limited the induction of donor-specific IFNγ-producing T cell alloimmunity without inducing Th2 or Th17 immunity in vivo and inhibited primed T cells from responding to donor antigens in secondary mixed lymphocyte responses.

Additional administration of anti-C5 mAb to the donor prior to graft recovery further prolonged graft survival and concomitantly reduced both the in vivo trafficking of primed T cells into the transplanted allograft and decreased expression of T cell chemoattractant chemokines within the graft. These results support the concept that C5 blockade can inhibit T cell-mediated allograft rejection through multiple mechanisms, and suggest that C5 blockade may constitute a viable strategy to prevent and/or treat T cell-mediated allograft rejection in humans.

Together, the data indicate that anti-C5 mAb functions as an adjuvant immunosuppressant to inhibit T cell activation and trafficking and to prolong murine cardiac allograft survival when used in conjunction with sub-therapeutic doses of CTLA4Ig. Because the data indicate that the combined use of CTLA4Ig and anti-C5 mAb is both safe (no untoward infections noted) and efficacious in mice, and because published studies support safety and preliminary efficacy of the analogous human reagents, future trials that include CTLA4Ig with anti-C5 mAb (potentially calcineurin-free) to prevent allograft rejection are warranted.

Consideration of the cellular source and local function of complement has potential therapeutic implications. Antibodies capable of blocking serum complement activation, including an anti-C5 antibody may be most beneficial to decrease post-transplant graft injury caused by alloantibody-initiated complement activation. Small molecule receptor antagonists, which are in development for human use, may better penetrate tissues to restrain downstream consequences of the released cleavage products (e.g. C3a and C5a) and thereby restrain complement's influence over immune cells. The recognition of the diversity through which complement participates in allograft injury supports the need for continued design and testing of complement inhibitors in human transplant recipients.