

Hypothesis

Dendritic cells and the mode of action of anticalcineurinic drugs: an integrating hypothesis

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Despite important advances in the understanding of the immunobiology of allotransplantation and the mechanism of action of immunosuppressive drugs, recent reports have challenged our current understanding of these phenomena.

Until now, the mode of action of cyclosporin A (CsA) and tacrolimus (FK506) has been mainly ascribed to their remarkable capacity to act upon T lymphocytes by inhibiting the production of IL-2 and IFN- γ , two cytokines required for the initiation and maintenance of T-lymphocyte responses in allograft rejection [1–3].

It is well recognized that immunosuppressive drugs such as CsA and FK506 act by inhibiting calcineurin activity. Calcineurin is a phosphatase that activates many transcription factors involved in cytokine transcription, including the upregulation of the mRNA for IL-2 [4]. Thus, the immunosuppressive effect of these drugs is that by inhibiting calcineurin they prevent IL-2 production and consequently T-cell activation.

Recently, Granucci *et al.* [5] reported that dendritic cells could produce a significant amount of IL-2 during activation. In fact, in these cells, the transition from resting to the activated state involves a very early and transient production of IL-2 mRNA and two waves of IL-2 protein production, each one coincident with the expression at the cell surface of MHC class II peptide and MHC class I peptide, respectively. Furthermore, they showed that dendritic cells from IL-2^{-/-}-deficient mice were seriously impaired in their capacity to induce T-cell proliferation [5]. In their report, Granucci *et al.* propose that the unique capacity of dendritic cells to stimulate naïve T cells and initiate an immune

response may be related to their capacity to produce IL-2 at early times after antigen uptake.

In addition, a recent report demonstrated that dendritic cells matured in the presence of the immunosuppressive drugs CsA or FK506 showed a diminished allostimulatory capacity in T-cell proliferation [6]. The authors could not ascribe this result to a direct effect on IL-2 or other cytokine.

Traditionally, dendritic cells act as professional antigen-presenting cells capable of initiating the immune response. Immature dendritic cells can take up and process soluble and particulate antigens and express at their surface peptide-loaded MHC class I and class II molecules as well as co-stimulatory molecules such as CD40, CD80 and CD86. Expression of these molecules is essential to the priming of CD4 and CD8 naïve T cells. As such, dendritic cells are likely to contribute to allorecognition and transplant rejection. In fact, dendritic cells from both graft and recipient have been considered deleterious to the graft [7]. However, recent advances have revealed that dendritic cells are also involved in the induction and maintenance of peripheral tolerance and graft acceptance [8,9]. This latter capacity of dendritic cells appears to be related to their state of maturation, since it has been shown that exposure of immature dendritic cells 7 days prior to transplantation to donor bone-marrow-derived cells can induce a specific and indefinite survival of fully allogeneic cardiac grafts [10]. It has been proposed that this effect may be due to the fact that immature dendritic cells are active in antigen uptake and processing but show low levels of co-stimulatory molecules like CD40 [11]. Alternatively, cytokine production like TNF- α and IL-12 may also be impeded [6].

Based on the newly reported production of IL-2 by dendritic cells and its postulated consequence on T-cell activation, and on the known effect of CsA and FK506 on IL-2 production, we would like to propose a complementary hypothesis to explain the immunosuppressive effect of these drugs. We hypothesize that these

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drugs, through their particular calcineurin-inhibiting function, inhibit IL-2 production by immature dendritic cells. As a consequence of this, dendritic cells will fail to efficiently mature, process and present alloantigens to T cells, thus interfering with T-cell activation. Furthermore, we would like to suggest that failure to activate alloreactive T cells should induce peripheral tolerance of these T-cell clones. If proved correct, this hypothesis will have an important impact on elucidating the pathophysiology of transplant rejection and the future treatment of transplant recipients. Of course the new mode of action of CsA and FK506 proposed here does not preclude a direct action of these drugs on T cells, as has been amply demonstrated. The mechanisms proposed here would explain the decrease of donor-specific T-cell clones that occurs after transplantation. In fact, during the course of organ transplantation, most rejection episodes occur during the first weeks after transplantation, a fact related to the number of donor-specific T-cell clones present in the graft [12–15]. A varying content of immature dendritic cells in donor liver, lung, heart or kidneys would partially explain different graft acceptability. Also, the proposed effect of IL-2 production by dendritic cells may to some extent explain the fact that dendritic cell-depleted kidney allografts are rejected at a slower rate than non-depleted grafts [16].

The proposed hypothesis assigns dendritic cells a new role in allograft acceptance, integrating the mode of action of CsA and FK506 with the tolerogenic function of immature dendritic cells and its newly described maturation-dependent IL-2 production.

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