

Tolerogenic dendritic cells induced by vitamin D receptor ligands enhance regulatory T cells inhibiting allograft rejection and autoimmune diseases

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Dendritic cells not only induce but also modulate T-cell activation and function. 1,25-dihydroxyvitamin D₃ (1,25(OH)₂D₃), the prototypic vitamin D receptor (VDR) ligand, is a hormone that induces dendritic cells with a tolerogenic phenotype, characterized by decreased expression of CD40, CD80, and CD86 costimulatory molecules, low interleukin (IL)-12 and enhanced IL-10 secretion [1]. We have found that a short treatment with 1,25(OH)₂D₃ induces tolerance to fully mismatched mouse islet allografts that is stable to challenge with donor-type spleen cells and allows acceptance of donor-type vascularized heart grafts. This effect is enhanced by coadministration of mycophenolate mofetil, a selective inhibitor of T- and B-cell proliferation, that has also effects similar to 1,25(OH)₂D₃ on dendritic cells [2]. Graft acceptance is associated with impaired development of type 1 CD4⁺ and CD8⁺ cells and an increased percentage of CD4⁺ CD25⁺ regulatory cells expressing CD152 in the spleen and in the draining lymph node. Transfer of CD4⁺ CD25⁺ cells from tolerant mice protects 100% of the syngeneic recipients from islet allograft rejection. CD4⁺ CD25⁺ cells that are able to inhibit the T-cell response to a pancreatic autoantigen and to significantly delay disease transfer by pathogenic CD4⁺ CD25⁻ cells are also induced by treatment of adult nonobese diabetic mice with 1,25-dihydroxy-16,23Z-diene-26,27-hexafluoro-19-nor vitamin D₃ (BXL-922). This treatment arrests progression of insulinitis and Th1 cell infiltration, and inhibits diabetes development at non-hypercalcemic doses [3]. The enhancement of CD4⁺ CD25⁺ regulatory T cells able to mediate transplantation tolerance and to arrest type 1 diabetes development by a short oral treatment with small organic compounds that induce tolerogenic dendritic cells, like VDR ligands, suggests possible clinical applications of this approach.

VDR ligands can inhibit not only acute but also chronic allograft rejection, as documented by inhibition of adventitial inflammation and intimal hyperplasia in murine aortic allografts [4]. While the prevention of leukocyte

infiltration into the adventitia is probably due to the immunomodulatory properties of VDR analogues, the inhibition of intimal cell proliferation, both endothelial and smooth muscle cells, is likely induced by their capacity to regulate cell growth. Thus, VDR ligands have pleiotropic immunoregulatory activities that are able to control allograft rejection. Antigen-presenting cells (APCs) and T cells can be direct targets of the hormone, leading to the inhibition of pathogenic effector T cells and enhancing the frequency of T cells with suppressive properties, largely via induction of tolerogenic dendritic cells [5]. These immunoregulatory activities, coupled with the absence of major side effects once calcemia is under control, have been translated into effective immunointervention in a variety of graft rejection models [6]. This body of knowledge represents a sound basis to further explore the immunoregulatory properties of VDR ligands in allograft rejection, and in particular in chronic rejection. Induction of tolerance to allografts remains an unfulfilled goal in clinical transplantation, and VDR ligands could be part of a tolerogenic regimen designed to achieve this goal.

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