

## Role of Tolerogenic Dendritic in Transplantation

Pierre Mordant\*

Department of Surgery, University of Paris, France

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The pursuit of clinical transplant tolerance has led to enhanced understanding of mechanisms underlying immune regulation, including the characterization of immune regulatory cells, especially antigen-presenting cells (APC) and regulatory T cells (Treg), which will play key roles in promoting operational tolerance. Dendritic cells (DC) are highly-efficient APC that are studied extensively in rodents and humans, and more recently in non-human primates. Due to their ability to manage both innate and adaptive immune responses, DC are considered to play crucial roles in directing the alloimmune response towards transplant tolerance or rejection. Mechanisms via which they will promote central and peripheral tolerance include clonal deletion, the induction of Treg, and inhibition of memory T cell responses. These properties have led to the utilization of tolerogenic DC as a therapeutic strategy to market transplant tolerance. In rodents, infusion of donor- or recipient-derived tolerogenic DC can extensively prolong donor-specific allograft survival, in association with regulation of the host T cell response. In clinical transplantation, progress has been made in monitoring DC in reference to graft outcome, including studies in operational liver transplant tolerance although clinical trials involving immune therapeutic DC for patients with cancer are ongoing, implementation of human DC therapy in clinical transplantation would require assessment of varied critical issues. These include cell isolation and purification techniques, source, route and timing of administration, and combination immunosuppressive therapy. With ongoing non-human primate studies focused on DC therapy, these logistics are often investigated seeking the optimal approaches. The scientific rationale for implementation of tolerogenic DC therapy to market clinical transplant tolerance is robust. Evaluation of technical and therapeutic logistic issues is a crucial next step before the appliance of "Therapeutic" DC in clinical organ transplantation.

### Introduction

In the absence of inflammation, tol DC maintain peripheral tolerance to self Ags through various inter-related mechanisms, including T cell deletion, induction of T cell anergy and induction of Treg, expression of immunomodulatory molecules, and production of immunosuppressive factors (e.g. IL-10; TGF $\beta$ ; and indoleamine dioxygenase). APC expressing IDO play a critical role in maintaining peripheral tolerance. Prolongation of pancreatic islet allograft survival in mice by soluble cytotoxic T lymphocyte-associated Ag 4 (CTLA 4) fusion protein (CTLA 4-Ig) requires intact tryptophan catabolism within the recipient, likely thanks to the power of CTLA4-Ig to upregulate IDO production by host DC. within the mouse spleen, an IDO+CD19+ DC subset exhibits a mature phenotype within the steady-state, and synthesizes high amounts of IDO that mediate T cell suppression. IDO+ CD19+ DC increase their production of IDO following CD 80/86 ligation by CTLA4 or TLR 9 ligation, and need autocrine release of IFN- $\alpha$  for signal transducer and activator of T cells (STAT) 1 activation and IDO up-regulation. Inhibition of IDO expression by silencing RNA (siRNA) inhibits DC-mediated suppression of T cell proliferation. Tryptophan-deprived DC show reduced capacity to stimulate T cells, express high

ILT 3 and LT 4, and induce suppressive CD 4+CD 25+Foxp3+Treg. In rodents, CD

103+DC in mesenteric lymph nodes and intestinal mucosa are shown to precise IDO. Inhibition of IDO activity induces Th1 and Th17 T cells in vivo, and prevents the event of Treg specific for oral Ags. In an autocrine manner, murine tolerogenic CD8+ DC secrete TGF- $\beta$  which maintains IDO activation. during a mouse model of collagen-induced arthritis, LPS-stimulated DC upregulate IDO expression, induce markers for Treg (Foxp3, TGF- $\beta$ 1 and CTLA-4) in vivo, and improve arthritis scores when injected after immunization.

The programmed death-1 (PD-1) receptor is an inhibitory molecule expressed on activated T cells and its ligands, PD-L1 and PD-L2, contribute to the negative regulation of T cell activation and peripheral tolerance. PD-1-PD-L1 interactions maintain peripheral tolerance by mechanisms distinct from those of CTLA-4. Ab-mediated blockade of PD-1 or PD-L1 leads to enhanced T cell-DC interaction and type I diabetes. It's been reported that PD-L1 and PD-L2 are expressed at very low levels on immature LC. Mature epidermal LC lack PD-1 expression, but express high levels of PD-L1 and PD-L2. Also, blockade of PD-L1 and/or PD-L2 on dermal DC leads to enhanced T cell activation. Thus, LC not only have tolerogenic properties, but even have regulatory functions which will counteract the pro-inflammatory activity of surrounding keratinocytes.

Heme oxygenase-1 (HO-1) is an intracellular enzyme that degrades heme and inhibits inflammation in vivo. Human DC dramatically decrease HO-1 expression during their maturation in vitro. Against this, cobalt protoporphyrin induction of HO-1 expression is related to downregulation of LPS-induced human DC maturation, secretion of anti-inflammatory cytokines, and inhibition of alloreactive T-cell proliferation. Also, induction of HO-1 inhibits the assembly of reactive oxygen species (ROS) induced by LPS in human DC, although their ability to supply IL-10 is maintained.

The non-classical MHC class I Ag HLA-G is expressed on human DC and T cells, and is involved in tolerance induction. HLA-G may be a key molecule within the regulation of allo-immune responses at the human fetal-maternal interface. It interacts with three inhibitory receptors: ILT2, ILT4, and killer T cell Ig-like receptor 2DL4 (KIR2DL4). HLA-G modulates immune responses through protection from NK cell- and cytotoxic T-lymphocyte-mediated cytolysis, inhibition of allogeneic T-cell proliferation, and modulation of DC function. HLA-G/ILT4 interaction promotes the event of tol DC.

\*Corresponding author: Pierre Mordant, Department of Surgery, University of Paris, France, E-mail: [pierremordant@php.fr](mailto:pierremordant@php.fr)

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During pregnancy, a population of immature decidual DC appears to differentially express specific intercellular adhesion molecule-3-grabbing non-integrin (DC-SIGN; a C-type lectin). Human DC-SIGN+ cells are CD83+CD25+mDC, with a high capacity to stimulate naive T-cell proliferation. DC-SIGN mDC appear during early pregnancy within the human endometrium and are closely related to inter-cellular adhesion molecule -3- expressing large granular lymphocytes (LGL), which are shown to supply high local concentrations of GM-CSF and IL-10. Thanks to the high affinity of DC-SIGN for ICAM-3, it's been suggested that interaction between these two cell populations (DC-SIGN+ and LGL) may prevent the interaction of DC-SIGN+ cells with T cells and further maturation of DC-SIGN into potent immunostimulatory DC.

### **Critical factors associated with clinical DC therapy**

A number of logistic issues got to be evaluated before implementation of therapeutic human tol DC. For instance, cell isolation and culture techniques for ex vivo preparation of tol DC can vary from one center to a different, which may end in significant variation in cell yield. Use of Ficoll isolation and cryopreservation may result during a higher pDC/mDC ratio than with fresh cells. Also, it's been shown that initial culture of human DC are often related to variability in surface molecule expression also as cytokine production. Additionally, materials used for clinical scale production of human DC during a "closed-system" are shown to affect cytokine production by DC, e.g. IL-10 and IL-12, which could affect their therapeutic potential in vivo after administration. This warrants technical standardization of DC preparation for clinical use.