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Review Article

Harnessing the properties of dendritic cells in the pursuit of immunological tolerance

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ABSTRACT

The acquisition of self-perpetuating, immunological tolerance specific for graft alloantigens has long been described as the "holy grail" of clinical transplantation. By removing the need for life-long immunosuppression following engraftment, the adverse consequences of immunosuppressive regimens, including chronic infections and malignancy, may be avoided. Furthermore, autoimmune diseases and allergy are, by definition, driven by aberrant immunological responses to ordinarily innocuous antigens. The re-establishment of permanent tolerance towards instigating antigens may, therefore, provide a cure to these common diseases. Whilst various cell types exhibiting a tolerogenic phenotype have been proposed for such a task, tolerogenic dendritic cells (tol-DCs) are exquisitely adapted for antigen presentation and interact with many facets of the immune system: as such, they are attractive candidates for use in strategies for immune intervention. We review here our current understanding of tol-DC mediated induction and maintenance of immunological tolerance. Additionally, we discuss recent *in vitro* findings from animal models and clinical trials of tol-DC immunotherapy in the setting of transplantation, autoimmunity and allergy which highlight their promising therapeutic potential, and speculate how tol-DC therapy may be developed in the future.

Immunologic tolerance is the specific absence of a destructive immune response to a specific antigen. Due to the inherently random nature of somatic recombination of T cell receptor (TCR) genes within developing thymocytes, a small population of mature thymocytes with self-reactive specificities persists following negative selection within the thymus. Mechanisms of self-tolerance, therefore, allow control of these hazardous autoreactive lymphocytes. The deliberate induction of tolerance to specific antigens may have important implications across a number of fields. Recently, exciting progress has been made in the use of tol-DCs in transplantation, autoimmunity and allergy. This review will describe the mechanisms of action of these tol-DCs and outline their use in the pre-clinical and clinical setting.

Mechanisms of DC-mediated tolerance

Since their discovery by Steinman and Cohn over 40 years ago, DCs have been predominantly viewed as immunogenic leukocytes, responsible for the coordination of powerful, antigen-specific immune responses distant from the site of antigen acquisition. In more recent history, these professional antigen presenting cells (APCs) have been shown to play a critical role

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in both the induction and maintenance of immunological tolerance. The extraordinary plasticity of phenotypes DCs can display, in addition to numerous DC subsets that have been described, are the predominant factors underlying their ability to produce apparently diametrically-opposed effects on the immune system.

The detection of pathogen- or damage-associated signatures by DCs during classical immune responses triggers substantial upregulation of gene products required for effective antigen presentation and effector T cell (T_{eff}) activation, including MHC Class II, CD80/86 and pro-inflammatory cytokines. Such changes are required to fulfil the three-stage activation of naïve T_{effs}: TCR engagement of cognate peptide-MHC (signal 1), ligation of costimulatory receptors (CD28) by costimulatory molecules (CD80 and CD86) (signal 2) and ligation of receptors with T cell stimulating cytokines (signal 3).

By contrast, tol-DCs are highly effective in antigen uptake, processing and presentation, but do not provide naïve T cells with the necessary costimulatory signals (signal 2) required for T_{eff} activation and clonal proliferation on engagement [Fig. 1]. In addition, whilst tol-DCs secrete only minimal amounts of interleukin (IL)-12, a critical component of signal 3, they produce large amounts of anti-inflammatory IL-10 and transforming growth factor (TGF)-β. Tol-DCs may actively induce and maintain tolerance through regulatory or deletional mechanisms. The discovery of autoimmune regulator (AIRE)-dependent autoreactive T cell deletion within secondary lymphoid tissues, in addition to the generation of natural T regulatory (T_{reg}) cells within the thymus has demonstrated a clear overlap between central and peripheral tolerance mechanisms [1]. A number of additional factors may contribute to or augment the ability of tol-DCs to establish tolerance.

Maturation status

Tol-DCs display an immature phenotype under steady state conditions and constitutively migrate throughout the periphery and lymphatic system, presenting self-antigen in the absence of costimulatory molecules. Immature, migratory DCs loaded with tissue antigens, such as those found in skin, are more effective at inducing antigen-specific FoxP3$^+$ T_{reg} cell populations than lymphoid resident DCs *in vivo*. This strongly suggests a role for migratory, immature DCs in promoting peripheral tolerance in the steady state [2].

Previous experiments have demonstrated that the maintenance of cells in an immature state, due to absence of maturation stimuli is associated with tolerance via induction of T cell deletion, anergy and polarisation towards a regulatory phenotype. The decision to polarize towards an immunogenic, or conversely, a tolerogenic phenotype may also be driven by whether DCs engulf necrotic or apoptotic cells. Upon engulfment of necrotic, stressed or virally infected cells, DCs become activated to stimulate both CD4$^+$ and CD8$^+$ T_{eff} responses [3]. In contrast, engulfment of healthy or apoptotic cells polarizes DCs to a tolerogenic state, resulting in the promotion of T cell anergy and death. Apoptotic cells, therefore, appear to be an insufficient stimulus for full DC maturation. Interestingly, immature DCs appear specialised for the uptake of apoptotic cells, and in doing so, acquire a tolerogenic phenotype that is resistant to maturation. Uptake of apoptotic DCs by immature DCs results in the generation of tol-DCs that have the potential to induce FoxP3$^+$ T_{reg} cells via TGF-β1 secretion [4].

Interestingly, recent studies have demonstrated that traditionally-matured DCs are capable of inducing and expanding T_{reg} cells [5]. It is possible, therefore, that the

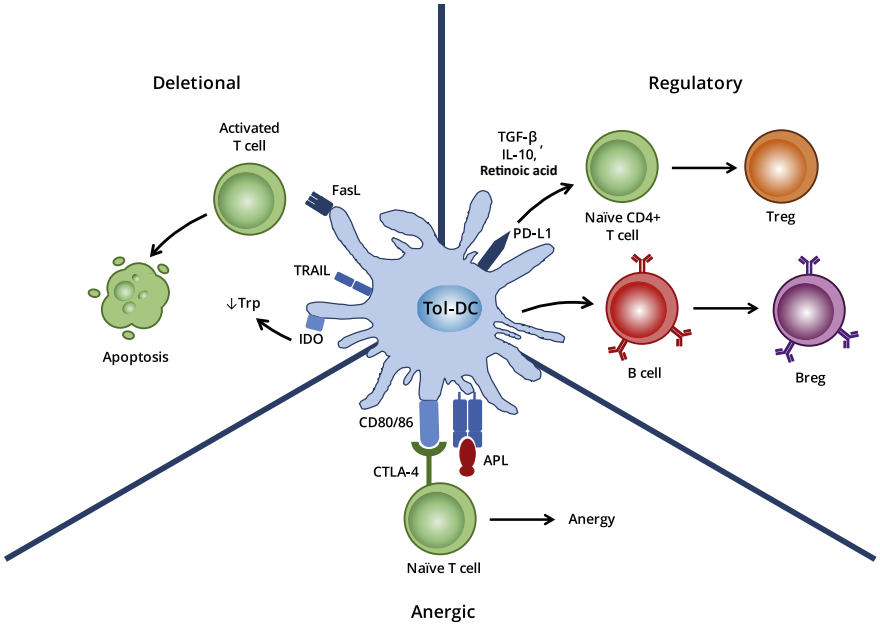

Fig. 1 Mechanisms of action of tol-DCs. The inhibition of T cell activation by tol-DCs has been attributed to various mechanisms that need not be mutually exclusive. These include Fas-FasL-mediated cell death of responding T cells, their functional paralysis through the induction of anergy or the polarisation of naïve T cells towards a regulatory phenotype through the secretion of anti-inflammatory cytokines such as IL-10 and TGF-β.