Dendritic cells and innate immunity in kidney transplantation

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This review summarizes emerging concepts related to the roles of dendritic cells (DCs) and innate immunity in organ transplant rejection. First, it highlights the primary role that recipient, rather than donor, DCs have in rejection and reviews their origin and function in the transplanted kidney. Second, it introduces the novel concept that recognition of allogeneic non-self by host monocytes (referred to here as innate allorecognition) is necessary for initiating rejection by inducing monocyte differentiation into mature, antigen-presenting DCs. Both concepts provide opportunities for preventing rejection by targeting monocytes or DCs.

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Kidney transplantation is the treatment of choice for patients with end-stage renal disease, but continuous suppression of the recipient's immune system is required to prevent rejection of the grafted kidney (renal allograft). Despite immunosuppression, long-term renal allograft outcomes remain suboptimal, with 10-year graft survival hovering around 45 and 60% for deceased and living donor kidneys, respectively.[1] A more thorough understanding of the mechanisms of graft rejection is therefore needed to improve outcomes without further increasing the burden of immunosuppression.

Allograft rejection is dependent on the activation of recipient T lymphocytes that recognize major or minor histocompatibility antigens expressed by donor, but not host, tissues (alloantigens).[2] Once activated, T lymphocytes reject the allograft by inflicting direct cytotoxicity on graft cells or by providing help to other cells of the immune system such as B lymphocytes, which differentiate into antibody-producing cells, and macrophages, which cause tissue inflammation. Therefore, a central question in transplantation immunology is how T lymphocytes are alerted to the presence of foreign tissue and how that leads to their activation. Here, we will attempt to answer these questions by reviewing the role of the innate immune system in initiating the T lymphocyte response after kidney transplantation, with particular emphasis on DCs whose principal functions are to present antigen and to provide essential costimulatory signals to T lymphocytes.

INNATE *VERSUS* ADAPTIVE

Mammalian immunity has long been defined through the adaptive features of T and B lymphocytes. Lymphocytes express somatically diversified receptors that recognize foreign antigens with high molecular specificity, expand clonally upon sensing antigen, and undergo further differentiation to generate short-lived effector and long-lived memory cells. This form of adaptation (clonal expansion, differentiation, and memory) ensures that the host is protected against microbial pathogens both acutely and in the long term, earning T and B lymphocyte responses the well-justified moniker 'adaptive immunity'. Although clearly essential for survival, adaptive immunity is also the reason why we reject life-saving allografts.

The initial and key requirement for mounting a successful adaptive immune response is activation of the T lymphocyte clone or clones specific for the non-self antigen. Seminal work in the 1980s established that full activation of T lymphocytes requires two molecular signals: one delivered by the T-cell receptor for antigen, which engages antigenic peptides presented in the grooves of major histocompatibility complex (MHC) molecules on activated antigen–presenting cells, namely DCs, and the other delivered by costimulatory and cytokine receptors whose ligands are also expressed by activated DCs.[3] An important question that lingered at the time, however, was the nature of the stimulus that induces quiescent DCs to acquire antigen-presenting and costimulatory functions.[4] The answer to this question unfolded rapidly with the discovery of pattern recognition receptors, a prime example being Toll-like receptors (TLR), which recognize pathogen-associated molecular patterns that are present in microbes but not in the host and cause activation of DCs.[5] This form of non-self recognition was dubbed 'innate immunity', as pattern recognition receptors are germline-encoded and are evolutionarily conserved, predating the emergence of adaptive immunity, and they are responsible for triggering many aspects of the inflammatory response that provides immediate protection against infection. Therefore, what role do DCs have in allograft rejection, and what are the innate immune mechanisms that lead to their activation after transplantation?

THE ROLE OF DENDRITIC CELLS IN ALLOGRAFT REJECTION

On a per-cell basis, activated DCs are the most effective antigen-presenting cells in mice and humans.[6] They are around 100-fold more potent at inducing the proliferation of allogeneic T cells in a mixed lymphocyte reaction and at presenting antigens to self-MHC-restricted T cells than their nearest relative, the macrophage. DCs are found in lymphoid and nonlymphoid tissues throughout the body, including the kidney,[7] and their numbers increase in the presence of inflammation. Inflammation also triggers the migration of DCs from nonlymphoid tissues to secondary lymphoid organs where they encounter and activate T lymphocytes. Therefore, organ transplants, unlike any other immune challenge, can potentially activate host T lymphocytes via two pathways: one is through alloantigens (usually intact allogeneic MHC molecules) presented 'directly' by donor DCs that accompany the transplanted organ, and the second is via alloantigens that have been taken up and processed by recipient DCs—a process referred to as 'indirect' allorecognition.[8,9] Which DC—donor or recipient—is essential for driving the alloimmune response, where do T lymphocytes encounter activated DCs after transplantation, and what are the consequences of this encounter?

Which DC: donor or recipient?

The precursor frequency of T lymphocytes with direct reactivity to non-self MHC molecules in mice and humans has been estimated to be as high as 5–10%, which is several orders of magnitude greater than that for conventional antigens.[10,11] This high precursor frequency, the presence of a significant number of donor DCs that express non-self MHC molecules within the transplanted organ, and the ability of donor DCs to induce potent proliferation of host T cells in the mixed lymphocyte reaction led to the hypothesis that donor DCs that travel from the allograft to the recipient's secondary lymphoid tissues after transplantation are the primary drivers of the alloimmune response.[12] Support for this hypothesis also derives from classical experiments showing that depletion of 'passenger leukocytes' from thyroid, pancreatic islet, or kidney allografts before transplantation resulted in their long-term survival in the host without the need for any immunosuppression.[13–17] Conversely, injection of donor DCs into the recipient of a DC-depleted kidney allograft restored acute rejection,[18] providing a cause–effect relationship between donor DCs and initiation of the alloimmune response.

Later studies, however, using murine heart, skin, and kidney transplantation models showed that donor DCs contribute to, but are not essential for, rejection. This was initially demonstrated by transplanting allografts from donors that lack MHC or costimulatory (CD80 and CD86) molecules[19–22]—thus rendering donor DCs incapable of activating T cells—and later by depleting grafts of DCs using targeted approaches.[23] Cahalan and co-workers[23,24] demonstrated that donor DCs that migrate out of transplanted organs are quickly surrounded and killed by NK cells in the secondary lymphoid tissues of the recipient, suggesting that intact donor DCs are unlikely to have a significant role in priming recipient T lymphocytes. Using the CD11c-DTR mouse model in which DCs can be selectively targeted and killed by diphtheria toxin, they also showed that depleting donor DCs in heart allografts did not delay rejection, whereas depletion of recipient DCs prolonged graft survival significantly.[23] The implication of these studies is that donor DCs, unlike what was previously suspected, are not essential for initiating alloimmune responses. Instead, donor and recipient DCs are either equally capable of performing the task or the latter are in fact the more important players.

How can one then reconcile the older data with the newer observations? An evolving concept is that donor DCs transplanted with the graft function as antigen-transporting, rather than as antigen-presenting, cells that deliver an antigenic cargo of non-self MHC molecules to recipient DCs.[8] This concept is supported by *in vitro*, as well as emerging *in vivo*, data that membrane fragments displaying intact MHC molecules are exchanged between DCs, a phenomenon known as 'cross-dressing' or 'semi-direct' antigen presentation, leading to the stimulation of T lymphocytes that recognize the transferred MHC.[25–27] Therefore, it is possible that after transplantation, both 'directly' and 'indirectly', alloreactive T lymphocytes are activated by recipient DCs: the former by recipient DCs that have acquired intact non-self MHC molecules from donor DCs and the latter by recipient DCs that have taken up donor alloantigens and processed