HHS Public Access

Author manuscript

Kidney Int. Author manuscript; available in PMC 2015 October 01.

Published in final edited form as:

Kidney Int. 2015 April ; 87(4): 712–718. doi:10.1038/ki.2014.430.

Dendritic Cells and Innate Immunity in Kidney Transplantation

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Summary

This review summarizes emerging concepts related to the roles of dendritic cells and innate immunity in organ transplant rejection. First, it highlights the primary role that recipient, rather than donor, dendritic cells 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 dendritic cells. Both concepts provide opportunities for preventing rejection by targeting monocytes or dendritic cells.

Keywords

acute rejection; ischemia reperfusion; lymphocytes

Introduction

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 ten-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

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Disclosures:
There are no interests to disclose.

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 dendritic cells (DCs) whose principal functions are to present antigen and provide essential co-stimulatory 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 (TCR), which engages antigenic peptides presented in the grooves of major histocompatibility complex (MHC) molecules on activated antigen presenting cells (APCs), 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 DC to acquire antigen presenting and costimulatory functions [4]. The answer to this question unfolded rapidly with the discovery of pattern recognition receptors (PRRs), a prime example being Toll-like receptors (TLR), which recognize pathogen-associated molecular patterns (PAMPs) present in microbes but not the host and cause activation of DCs [5]. This form of non-self recognition was dubbed “innate immunity” as PRRs are germline-encoded and are evolutionarily conserved, predating the emergence of adaptive immunity, and are responsible for triggering many aspects of the inflammatory response that provides immediate protection against infection. So what role do DCs play 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 APCs 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 (MLR) and at presenting antigens to self MHC-restricted T cells than their nearest relative, the macrophage. DCs are found in lymphoid and non-lymphoid

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 non-lymphoid 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 then – 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%, 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 MLR 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 prior to 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 co-stimulatory (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 coworkers 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 [23, 24], suggesting that intact donor DCs are unlikely to play 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 while 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 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 them for presentation in the context of self-MHC molecules. Additional *in vivo* data are still needed to validate this concept, but such data are likely to emerge in the near future.

Where do T lymphocytes encounter activated DCs?

Immunologists have traditionally focused on DC-T lymphocyte encounters in secondary lymphoid organs (the spleen, lymph nodes, and mucosal lymphoid tissues) because these are the key sites where primary immune responses take place. Naïve and a subset of memory T lymphocytes, so-called central memory T lymphocytes, home to secondary lymphoid tissues by virtue of their expression of the chemokine receptor CCR7 [28]. There they make stable contacts with and are activated by DCs that present the antigens which they recognize. Earlier studies demonstrated that acute allograft rejection in an immunologically naïve animal is indeed dependent on T lymphocyte activation within secondary lymphoid tissues [29]. Later studies, however, uncovered exceptions to this rule. First, it was demonstrated that memory T lymphocytes cause allograft rejection in the absence of secondary lymphoid tissues [30], consistent with the ability of both central and effector memory T lymphocytes to home to and proliferate at non-lymphoid sites [31]. Second, it was shown that the acute rejection of certain types of allografts, namely lung and full-thickness or vascularized skin transplants, is not dependent on secondary lymphoid organs, even in immunologically naïve recipients [32–34]. The latter observations can be explained by the presence of bronchio-alveolar lymphoid tissues (BALT) that readily support naïve T cell activation by DCs in the lung, and to the rapid induction of endothelial peripheral node addressin (PNAd) in neovascularized full-thickness skin grafts that enable naïve T cells to enter the DC-rich dermis [35]. Therefore, alloimmune responses are initiated in either host secondary lymphoid tissues or in the graft itself depending on the type of organ transplanted and the type of T lymphocyte (naïve *vs* memory) involved. The role of memory T lymphocytes in initiating the rejection response is germane to the clinical setting because alloreactivity in humans is not restricted to the naïve T lymphocyte repertoire but is equally represented in the memory pools [10, 36].

DCs in the transplanted kidney: continuous love affair with the T cell

In addition to T lymphocyte-DC interactions within secondary lymphoid tissues, it is now accepted that activated T lymphocytes interact with DCs outside secondary lymphoid organs [37], raising several important question in transplantation: Do memory or effector T cells that migrate to an allograft contact DCs there? If they do, which DCs and what functions do these contacts serve? Intra-vital imaging of lung and skin allografts in the mouse has demonstrated that host T cells make stable contacts with DCs within the graft

tissue [32, 38], but did not establish the role of these interactions. Using similar imaging technology, we have recently shown that the majority of anti-donor effector T cells that migrate to a transplanted kidney engage in prolonged, stable contacts with DCs in the graft [39]. The contacts occurred within the lumina of post-capillary venules, specifically with the dendrites of perivascular DCs that reach into the bloodstream, and in the interstitium of the renal cortex. Stable contacts between T lymphocytes and graft DCs within vascular lumina caused T lymphocyte arrest and transmigration across the endothelium. This previously unappreciated function of graft DCs is dependent on presentation of cognate antigen by the DC to the T lymphocyte but is independent of chemokine signaling via $G\alpha_i$-coupled receptors [39]. Therefore, graft DCs play a prominent role in mediating the migration of donor antigen-specific T lymphocytes into the transplanted kidney and, quite likely, their subsequent retention in the interstitium (see below). Based on studies in viral infection models [40] and emerging data in a kidney transplantation model (Zheng & Lakkis, unpublished), it is possible that cognate interactions between graft DCs and T lymphocyte are also important for memory T cell recall and further activation of effector T cells within the graft. Therefore, the relationship between DCs and T lymphocytes is not restricted to a one-night stand in secondary lymphoid organs but is one that blossoms into a protracted love affair in the target non-lymphoid tissue. In transplantation, this implies that interrupting T lymphocyte-DC interactions in the graft could provide an opportunity to prevent or reverse rejection in a cognate, donor-specific manner.

Which DC is then responsible for engaging effector and memory T cells within the transplanted kidney? It has long been known that donor DCs that accompany the graft emigrate out of the graft and can be detected in the recipient's secondary lymphoid organs, at least in the immediate period after transplantation [12, 41]. However, the rate and extent by which donor DCs are replaced by recipient DCs and the lineage of the recipient DCs that populate the graft has not been carefully elucidated. Recent work from our laboratory has shown that the majority of donor DCs in mouse kidney and heart grafts are replaced by recipient DCs within one day after transplantation (Zheng & Lakkis, unpublished). In kidney grafts, donor DCs represented less than 10% of all DCs by day seven after transplantation, while in heart grafts the proportion was even lower. DC replacement occurred in both allogeneic and syngeneic grafts, but the absolute number of recipient DCs was approximately 40-fold higher in the former. The vast majority of recipient DCs present in a transplanted kidney or heart were derived from monocytes and had a mature phenotype – they expressed high levels of MHC class II and costimulatory molecules (e.g., CD80). Moreover, effector T cells that infiltrated kidney grafts made stable, cognate interactions with recipient monocyte-derived DCs. Depletion of monocyte-lineage cells in the host at the time of transplantation significantly reduced the T lymphocyte infiltrate, indicating that DCs of recipient origin play an important role in T lymphocyte migration and retention in the graft [42]. These findings provide support for targeting recipient DCs that populate the graft or targeting their precursor, the monocyte, as a novel means to prevent rejection.

The Role of the Innate Immune System in Allograft Rejection

The process of transplanting an organ from one individual to another is associated with significant inflammation in the graft caused mainly by ischemia-reperfusion injury. There is

ample evidence to indicate that this form of inflammation potentiates the host's adaptive alloimmune response through myriad molecular and cellular mediators [43, 44]. These include small molecules such as free oxygen radicals, uric acid, and nucleic acids; lipid products such as prostaglandins and leukotrienes; protein molecules such as the complement system and HMGB1; and myeloid cells such as neutrophils, macrophages, and DCs. Many of these mediators influence not only the afferent (activation) phase of the adaptive alloimmune response but also its effector arm by enhancing T lymphocyte migration into the graft and the tissue damage that ensues. Therefore, broadly defined to include inflammation, innate immunity is an important contributor to allograft rejection. However, is innate immunity necessary or sufficient for rejection, and if necessary, is the innate immune response to an allograft solely an inflammatory response caused by the transplantation procedure (ischemia-reperfusion injury) or is it a response to non-self determinants present in allogeneic but not self-tissues?

The innate immune system: necessary or sufficient?

That the innate immune system is not sufficient for allograft rejection is well established. Many studies have shown that T lymphocyte-depleted humans or experimental animals do not mount an acute rejection response until T lymphocytes have returned to the circulation [45, 46]. A recent analysis of cardiac allografts transplanted to *RAG*$^{-/-}$ mice, which lack T and B lymphocytes but have an intact if not heightened innate immune system, confirmed that innate immunity alone does not lead to either acute or chronic rejection [47]. In the same study, injecting adjuvants to stimulate the innate immune response of *RAG*$^{-/-}$ mice, or reconstituting the mice with 'innate' B-1 lymphocytes to generate natural IgM antibodies, failed to recapitulate rejection. Some mouse studies, however, have suggested that NK cells, which belong to the lymphoid lineage and share adaptive features with lymphocytes, are sufficient for causing chronic rejection if their number and function are enhanced by concomitant viral infection or exogenous cytokines [48, 49]. Moreover, a small cohort of patients profoundly depleted of T lymphocytes at the time of kidney transplantation, but not given any maintenance immunosuppression, experienced transient decline in graft function around one month after transplantation - at a time when circulating T cells were present in only very small numbers [50]. Graft biopsies in these patients revealed a predominantly monocytic infiltrate. The experimental and human data therefore establish that the innate immune system contributes to rejection but is not sufficient for causing it.

Whether innate immune activation is necessary for allograft rejection is a more difficult question to answer. First, experimental animals that lack an innate immune system but have functional adaptive immunity do not exist (for one, such animals will likely not survive beyond the early neonatal period). Second, the great breadth and redundancy of innate immune mediators preclude testing all of them at once. Nevertheless, emerging data have begun to ascertain whether general components or features of innate immunity play key roles in allograft rejection. These will be reviewed next.

The danger hypothesis

The danger hypothesis was proposed in 1994 by Matzinger as an alternate to Janeway's PRRs/PAMPs model of innate immunity to account not only for antimicrobial immune

responses but also for robust responses that arise in the absence of obvious microbial adjuvants, a prime example being transplantation [51]. In its most contemporary iteration, this hypothesis states that innate immune cells recognize danger-associated molecular patterns (DAMPs) released from stressed or dying cells, whether cell stress or death is caused by infection, ischemia, or other forms of injury. Many DAMPs have been identified, all of which induce inflammation and in some cases potentiate adaptive immunity to foreign antigens, including alloantigens [52, 53]. Most, if not all, identified DAMPs appear to mediate their inflammatory actions via known PRRs that recognize microbial products, most commonly via TLR4. The role of TLR4 in ischemia-reperfusion injury of transplanted organs has been established in experimental animals and humans [54].

One shortcoming of the danger hypothesis is the possibility that DAMPs, although potent inducers of inflammation and ischemia-reperfusion injury, are not sufficient for triggering robust adaptive immune responses as PAMPs do. Sporri and Reis e Sousa reported that indirect activation by inflammatory mediators generated DCs that supported CD4 T lymphocyte clonal expansion but failed to direct T helper cell differentiation, mainly because the DCs failed to produce IL-12 [55]. In contrast, exposure to PAMPs resulted in fully activated DCs that produced IL-12 and promoted T helper responses. In transplantation, additional evidence suggests that danger may not be necessary for triggering allograft rejection. For example, the rejection of allografts mismatched with the recipient at major and/or multiple minor histocompatibility antigens occurs without significant delay in the absence of innate signaling pathways or cytokines that mediate the action of DAMPs [56–60]. Likewise, allografts parked in T lymphocyte-deficient mice are rejected when the host is replenished with T lymphocytes long after tissue injury has resolved [61–65], implying that danger is not necessary for triggering rejection or that unaccounted for danger or microbial stimuli persist in these recipients. An alternative explanation is that additional innate stimuli that are responsible for “full” DC activation exist in the setting of organ transplantation. If so, what could these stimuli be?

Innate sensing of allogeneic non-self

Examples of ancient allorecognition systems that predate the evolution of adaptive immunity abound in nature [66, 67]. This fact has long suggested the possibility that mammalian innate immune systems have retained the ability to recognize allogeneic non-self, presumably to alert the host to harmful non-microbial invaders such as stem cells from the fetus or transmissible tumor cells from another individual [47]. Our group has formally tested the possibility that the mouse innate immune system distinguishes between self and allogeneic non-self in a manner analogous to its ability to differentiate between self and microbial non-self [68]. Zecher et al showed that injecting allogeneic *RAG*$^{-/-}$ splenocytes into the ear pinnae of *RAG*$^{-/-}$ recipinets elicits significantly greater swelling and infiltration of the skin with host myeloid cells than injecting syngeneic splenocytes [69]. Depletion and cell transfer experiments established that the response is independent of NK cells and, instead, is mediated by monocytes [69]. These studies provided direct evidence that the mouse innate immune system is capable of distinguishing between self and allogeneic non-self. However, they did not establish the biological significance of such innate sensing and what its consequences are for allograft rejection.

By performing heart, kidney, and bone marrow transplants into $RAG^{-/-}\gamma c^{-/-}$ mice, which lack T, B, NK and innate lymphoid cells, we have now established that innate sensing of allogeneic non-self is necessary for initiating alloimmunity [42]. In these experiments, allogeneic grafts elicited persistent differentiation of monocytes to mature DC that expressed IL-12 and stimulate T cell proliferation and IFNγ production. In contrast, syngeneic grafts elicited transient and less pronounced differentiation of monocytes to DC, which neither expressed IL-12 nor stimulate IFNγ production. In a heart transplantation model where T cell recognition is restricted to a single foreign antigen on the graft, rejection occurred only if allogeneic non-self was also sensed by the host's innate immune system. Therefore, danger alone, which is common to both syngeneic and allogeneic grafts, is not sufficient for inducing "full" DC activation. Instead, innate recognition of allogeneic allogeneic non-self by monocytes is required for this process and for initiating T lymphocyte-dependent alloimmunity. These concepts are summarized schematically in Figure 1. The mechanisms by which monocytes recognize allogeneic non-self and the nature of the allodeterminants that trigger monocyte differentiation to mature DC have not been identified yet. Elucidating these mechanisms should provide the possibility of matching between donors and recipients at innate allodeterminants to improve graft outcomes or of interrupting innate allorecognition pathways to prevent acute or chronic rejection.

Concluding Remarks and Therapeutic Prospects

In this review we did not aim at providing a comprehensive review of the literature on the roles of DCs and the innate immune system in kidney transplantation but at emphasizing two emerging concepts in this area. First is the concept that recipient DCs, specifically those derived from monocytes, are increasingly being recognized as key players in allograft rejection. They have a primary role in T lymphocyte activation, migration, and retention in the graft. Second is the novel concept that monocytes distinguish between self and allogeneic non-self and by doing so, trigger allograft rejection and perpetuate it. Danger stimuli, although important in ischemia-reperfusion injury, are not sufficient for initiating alloimmunity.

We believe that both concepts should provide valuable opportunities in the future to inhibit alloimmune responses in a cognate and safe manner. The first provides the prospect that inhibiting recipient monocyte migration to the graft or their differentiation into DCs could interrupt rejection even after T cell priming has already taken place in secondary lymphoid tissues (for example, rejection mediated by memory T cells). The second, the innate allorecognition concept, raises the possibility that identifying the mechanisms by which monocytes sense allogeneic non-self could lead to novel matching schemes between donors or recipients to minimize rejection, especially chronic rejection which becomes manifest long after danger stimuli have subsided. Alternatively, blocking the signaling pathways triggered by the recognition of allogeneic non-self by monocytes would constitute a potentially novel and unexplored therapeutic modality in transplantation.

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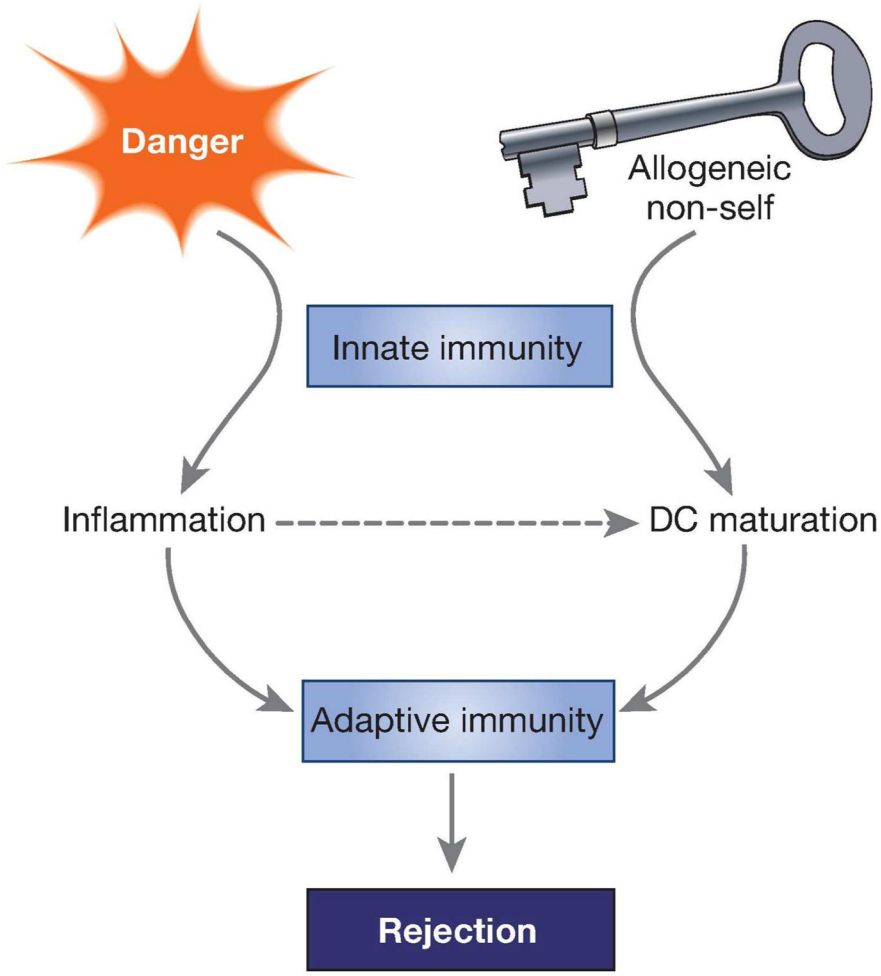

Figure 1. Innate allorecognition and danger link innate to adaptive immunity after transplantation

Recognition of allogeneic non-self by recipient monocytes is *key* for generating mature DC that drive graft rejection by T lymphocytes. Danger, which causes inflammation in the graft but is not sufficient for driving rejection, is nevertheless essential for potentiating the adaptive alloimmune response.