REVIEW

Recall features and allorecognition in innate immunity

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SUMMARY

Alloimmunity traditionally distinguishes short-lived, rapid and nonspecific innate immune responses from adaptive immune responses that are characterized by a highly specific response initiated in a delayed fashion. Key players of innate immunity such as natural killer (NK) cells and macrophages present the first-line defence of immunity. The concept of unspecific responses in innate immunity has recently been challenged. The discovery of pattern recognition receptors (PRRs) has demonstrated that innate immune cells respond in a semi-specific fashion through the recognition of pathogen-associated molecular patterns (PAMPs) representing conserved molecular structures shared by large groups of microorganisms. Although immunological memory has generally been considered as exclusive to adaptive immunity, recent studies have demonstrated that innate immune cells have the potential to acquire memory. Here, we discuss allospecific features of innate immunity and their relevance in transplantation.

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Introduction

The cascade of responses to injury, pathogens or alloantigens traditionally distinguishes innate and adaptive immunity. Innate immune responses are based on a variety of defence mechanisms that include the complement system and cellular responses executed by macrophages, neutrophils and NK cells. In general, innate immune cells have been considered short-lived with the capacity to respond rapidly and in a nonspecific fashion against pathogens. Characteristically, innate immune cells can detect and kill pathogens within minutes or hours as they do not rely on clonal expansion [1]. Adaptive immunity, in contrast, is characterized by a highly specific response initiated in a delayed fashion. As a basis for their specificity, adaptive immune cells express a highly diverse repertoire of receptors that recognize antigens with high molecular specificity based on a highly diverse and specific repertoire of immunoglobulins and T-cell receptors with the rearrangement of variable (V), joining (J); in some cases diversity (D) gene segments occurring in early stages of T- and B-cell maturation play an additional role. During an initial activation of T and B cells, some cells differentiate into memory B and T cells. Upon interaction with a previously encountered antigen, these memory cells mount a more potent and rapid immune response

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characterizes immunological memory of the adaptive immune system. [2].

Innate lymphoid cells as a link between innate and adaptive immunity

Natural killer cells are bone marrow-derived large granular cytotoxic lymphocytes with the ability to kill tumour cells in addition to virus-infected cells without the need of prior immunization or activation [3]. NK cells are known to differentiate and mature in the bone marrow and are primarily found in the spleen, liver, lung and peripheral blood. Limited numbers of NK cells are also localized in the thymus, bone marrow and lymph nodes [4]. Effector mechanisms of NK cell are communicated through cytotoxic granules containing perforin and granzymes that perforate the membrane of target cells, inducing apoptosis [5]. Indeed, the term 'natural killer' has been derived from the spontaneous cytotoxic capacity of this cell population.

Recently, innate lymphoid cells (ILCs) that lack a recombined antigen receptor have been identified, further blurring the traditional conceptual boundaries between innate and adaptive immunity [6]. These 'innate' lymphocytes are thought to play a role as a functional bridge between innate and adaptive immune defences.

NK cells have been characterized as prototypical cells of group 1 innate lymphoid cells (ILCs) [7]. ILCs play an important role during infection, inflammation and tissue homoeostasis and have been categorized into three groups based on their cytokine production and transcription factors. Group 1 ILCs (ILC1s), including NK cells, are defined by the production of IFNγ and the expression of the transcription factor T-bet. Group 2 ILCs (ILC2s) produce IL-5 and IL-13 and depend on the transcription factor GATA-binding protein 3 (GATA3) that expresses the retinoic acid receptor-related orphan receptor-α (ROR-α). Group 3 ILCs (ILC3s) produce IL-17 and/or IL-22 and are dependent on the transcription factor RORγt. Although specific cell surface markers, transcription factors and cytokine have been characterized for ILC2s and ILC3s, additional studies are required for their classification and ultimately for a better understanding of their role in linking innate and adaptive immunity.

Key players of innate immunity

Both, NK cells and macrophages are part of the innate immune system and play key roles as a first-line defence against viral infections, tumours and microbes. Unlike T and B cells, NK cells lack the ability to undergo somatic receptor gene rearrangements assumed hitherto to prevent innate memory responses upon a second encounter with the same pathogen. Memory as part of adaptive immunity, in contrast, has been linked to a clonotypic proliferation of antigen receptors in T and B cells. Recently, however, the concept of absent memory functions in innate immunity has been challenged by evidence showing that certain subsets of mouse NK cells and macrophages may display memory characteristics.

Although the impact of innate immune responses and the communication between innate and adaptive immunity has been increasingly recognized, adaptive immunity has been considered as the main driver in allograft rejection. Of note, recent studies have demonstrated that NK cells and macrophages play important roles in allograft rejection [8]. Importantly, NK cells and macrophages have been shown to have adaptive capacities shaping their potential for allorecognition and memory [9,10].

Antigen recognition

NK cells can discriminate between normal cells, aberrant virus-infected and tumour cells through the integration of signals derived from activating or inhibitory receptors. The capacity of NK cells to recognize alloantigens has until recently been characterized as nonmajor histocompatibility complex (MHC)-restricted because NK cells attack target cells that either lack MHC or express various allogeneic MHC molecules. Based on the 'missing-self' hypothesis NK cells are activated by the absence of self-MHC molecules on the surface of their target cells[11]. A common misconception has been that NK cells attack any cell lacking MHC-I. Additional studies revealed how NK cells kill tumours that express MHC-I or how autologous cells with absent MHC-I expression escape NK cells. In fact, the recognition of 'missing-self' is mediated by a variety of inhibitory receptors triggered by MHC-I antigens on the cell surface[12]. NK cells remain inactive when inhibitory receptors recognize MHC-I on normal cells. However, when NK cells encounter abnormal cells that lack MHC-I, inhibitory receptors remain silent while activating signals prevail. Principal inhibitory components include diverse repertoires of Ly49 receptors on murine NK cells, killer cell immunoglobulin-like receptors (KIR) on human NK cells, and CD94/NKG2A on both murine and human NK cells [5]. In addition to inhibitory signals, NK cells express various activating receptors. Prototypic examples of activating receptors include

NKG2D and NKp46 that recognize antigens on virus-infected and tumour cells. Binding of NKG2D ligands, such as retinoic acid early inducible-1 gene (RAE-1) in mice, and major histocompatibility complex class I chain-related gene A and gene B (MICA/B) in humans augment proliferation, cytotoxicity, and the production of cytokines and chemokines [12]. When both inhibitory and activating receptors engage at the same time, effector functions of NK cells will be determined by the net balance of signals. Therefore, NK cells can recognize and attack a diversity of aberrant cells without damaging normal cells.

Macrophages have traditionally been characterized as phagocytotic cells that engulf and digest invading microorganisms. Charles Janeway postulated in 1989 that innate immunity senses pathogens utilizing receptors termed pattern recognition receptors (PRRs) [13]. *Drosophila* strains that carry a loss-of-function in the *Toll* gene demonstrated high susceptibility to fungal infections linked to defective induction of antifungal peptides [14]. Accumulating evidence suggests that germ-line-encoded PRRs can recognize a wide range of pathogens. PRRs that recognize pathogen-associated molecular patterns (PAMPs) representing conserved molecular patterns shared by large groups of microorganisms are expressed not only on macrophages but also on dendritic cells (DCs) and neutrophils [15]. Pattern recognition receptors are classified into four different groups based on their cellular localization and function and include transmembrane proteins such as Toll-like receptors (TLRs), C-type lectin receptors (CLRs), cytoplasmic proteins such as NOD (nucleotide-binding oligomerization domain-containing protein)-like receptors (NLRs) and Retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs). TLRs, for example, recognize a variety of microbial components such as microbe-specific lipoproteins, glycolipids, proteins and nucleic acids. Downstream of PPR ligation, pathways that mediate innate immune and inflammatory responses become activated in monocytes and dendritic cells. Subsequently, pro-inflammatory cytokines and chemokines are produced, and leucocytes become mobilized and activated. Recent studies indicate that PRRs are not only involved in recognizing pathogens but also in recognizing endogenous molecules released by damaged cells, so-called damage-associated molecular patterns (DAMPs) that include nucleic acids, uric acid, β-amiroid and cholesterol [16]. Clinically, the recognition of these endogenous ligands by PRRs is associated with a variety of chronic inflammatory and autoimmune diseases.

Memory and recall capacities

Immunological memory characterizes the ability of immune cells to recall a previous encounter with a pathogen while providing an enhanced response upon secondary contact with the same pathogen. Although immunological memory has generally been considered as mediated exclusively by T and B cells, recent studies indicate that NK cells may also have memory capacities. Accumulating evidence indicates that NK cells can initiate memory-like responses to certain antigens. In experimental models, murine cytomegalovirus (MCMV) infection in C57Bl/6 mice induced antigen-specific NK memory cells (Fig. 1a) [17]. In this model, MCMV facilitated the expansion of NK cells that express the Ly49H receptor capable of recognizing the m157MCMV protein on infected cells. Those NK cells were able to survive up to 70 days while undergoing robust expansion with a display of enhanced cytotoxicity and cytokine responses subsequent to a secondary MCMV challenge. In another model, in vitro stimulation of NK cells with Interleukin-12 (IL-12), IL-15 and IL-18 indicated the capacity of memory responses (Fig. 1b) [18]. Indeed, when stimulated NK cells were transferred into naïve $Rag1^{-/-}$ mice that lack T and B cells, a robust Interferon–gamma (IFNγ) production upon restimulation had been observed. Of note, mechanisms by which cytokine signalling induce memory-like properties in NK cells remain unknown. Moreover, hepatic NK cells have been shown to mediate antigen-specific memory in a model of hapten-induced contact hypersensitivity (CHS) and viral infection (Fig. 1c) [10]. CHS is a form of delayed-type hypersensitivity (DTH) induced by chemical haptens and observed for at least 4 weeks subsequent to the hapten encounter. When NK cells derived from livers of hapten-sensitized mice were adoptively transferred into naïve $Rag2^{-/-}Il2rg^{-/-}$ mice lacking T-, B- and NK cells, animals revealed an augmented response to CHS. Subsequent work by the same group indicated that DTH responses of NK cells are not only effective when encountering haptens but also towards virus-like particles of influenza, vesicular stomatitis virus (VSV) and human immunodeficiency virus (HIV) (Fig. 1c) [19]. Adoptive transfer of virus-sensitized hepatic NK cells into naïve $Rag2^{-/-}Il2rg^{-/-}$ mice enhanced survival after a lethal challenge with the sensitizing virus. Interestingly, the chemokine receptor CXCR6 played a critical role in hepatic NK cells contributing to the persistence of recall functions but not antigen recognition.

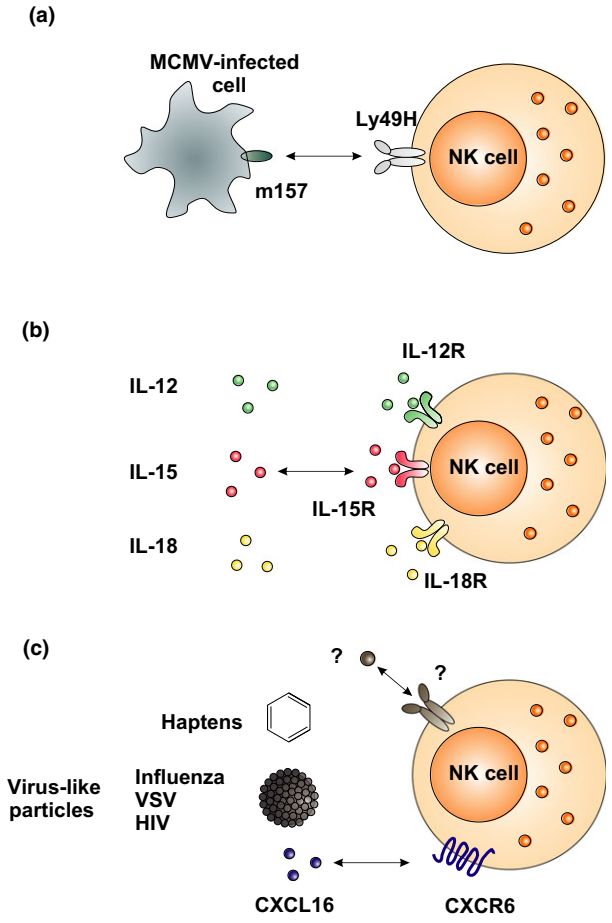

Figure 1 NK cells may have memory capacities. (a) MCMV infection in mice induces antigen-specific NK memory cells. In this model, MCMV expanded a subpopulation of NK cells that express the Ly49H receptor capable of recognizing the m157MCMV protein on infected cells. (b) Memory NK cells are induced after exposure to IL-12, IL-15, and IL-18 in mice. (c) CXCR6$^+$ NK cells isolated from mouse livers mediate antigen-specific memory responses against haptens and virus-like particles of influenza, VSV and HIV. HIV, human immunodeficiency virus; MCMV, murine cytomegalovirus; VSV, vesicular stomatitis virus.

Moreover, recent studies have revealed several novel molecular pathways involved in regulating memory capacities of NK cells. The zinc finger (BTB-ZF) transcription factor Zbtb32, for example, is essential for antigen-specific proliferation and protective capacities of MCMV-specific NK cells[20]. BTB-ZF proteins are an evolutionarily conserved large family of transcriptional regulators involved in biological processes such as lymphocyte differentiation and malignant transformation [21,22]. Increasing evidence also suggests that signals from pro-inflammatory cytokines induce Zbtb32 expression in NK cells [20]. More recent data have shown that FcRγ-deficient NK cells have memory capacities in an antibody-dependent manner in human cytomegalovirus (HCMV)-infected individuals [23]. This study also demonstrated that several distinct subsets of memory-like NK cells are associated with deficiencies of multiple transcription factors and signalling proteins including the tyrosine kinase SYK. SYK deficiency, at the same time, has been correlated with hypermethylation of a specific region in the SYK promoter DNA sequences. These findings indicate that memory-like NK cells can be induced by epigenetic modification.

Moreover, several recent studies provide evidence that macrophages/monocytes display memory characteristics with, for example, monocytes demonstrating recall responses to microbial components after preexposure to *Candia albicans* or β-glucans (Fig. 2a) [24–26]. Clinically, monocytes mediated NOD2-dependent nonspecific protection subsequent to a vaccination with Bacille Calmette–Guérin (BCG) via epigenetic reprogramming suggested that infections and inflammatory stimuli can mediate lasting changes within the properties of macrophages (Fig. 2b) [27].

Additional studies found recall features of other innate immune cells including γδ T cells and natural killer T (NKT) cells. A distinct subset of mucosal γδ T cells that responded to oral Listeria monocytogenes developed memory responses in the murine intestinal mucosa [28]. Here, mucosal γδ T cells were able to survive long-term undergoing a robust expansion against secondary infections while displaying an enhanced production of IFN-γand IL-17A. A more recent study showed that invariant natural killer T cells (iNKT cells) defined as KLRG1$^+$ (Killer cell lectin-like receptor subfamily G, member 1–positive) residing in the lung of mice have memory capacity [29]. KLRG1$^+$ iNKT cells immunized with α-Galactosylceramide (α-GalCer) loaded CD1d$^+$ DCs (DC/Gal) survived for several months in the lung. Moreover, these KLRG1$^+$ iNKT cells showed more robust expansion by rechallenging with DC/Gal compared to naïve iNKT cells.

Innate immunity in transplantation

Until recently, the role of NK cells in allograft rejection had received only little attention. Severe combined immunodeficiency (SCID) or recombination activating gene (RAG) knockout mice that lack T and B cells but retain intact NK cell function have been unable to mount a rejection subsequent to the transplantation of cardiac and skin allografts [30–32]. Recent studies, however, have indicated that activated NK cells play a critical role in alloimmunity. Activated NK cells produce inflammatory cytokines such as IFN-γ that stimulate T

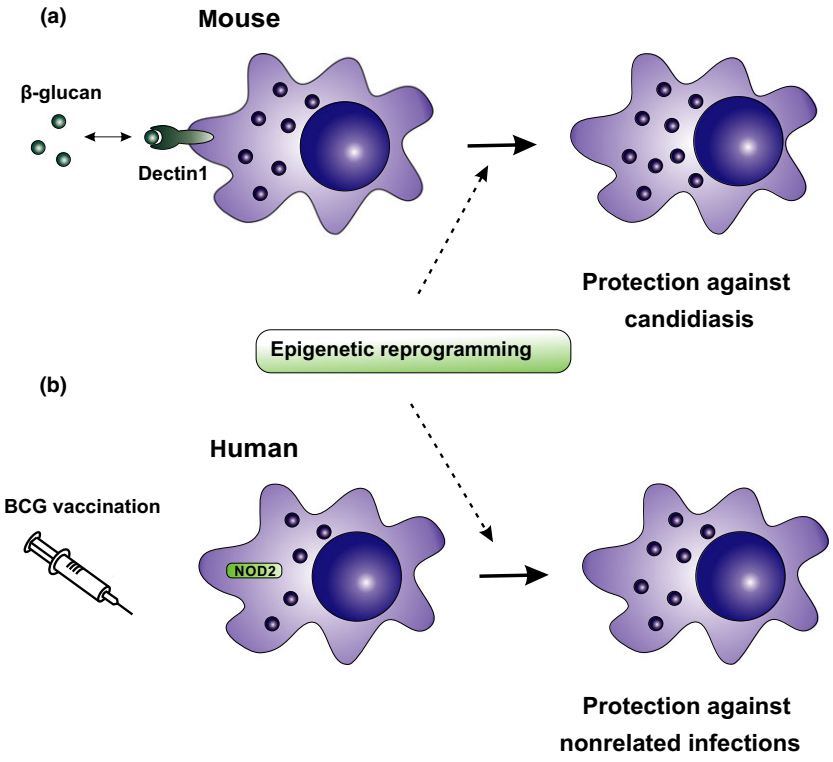

Figure 2 Macrophages display memory characteristics. (a) A previous infection with *Candida albicans* induces protection against reinfection through epigenetic reprogramming of monocytes in mice. (b) BCG vaccination induces memory-like characteristics in human monocytes and establishes nonspecific protection from infections in a NOD2-dependent manner. BCG, Bacille Calmette-Guérin; NOD, nucleotide-binding oligomerization domain-containing protein.

cells. Through their direct cytotoxic functions, NK cells have furthermore the capacity to eliminate allogeneic cells. More recent evidence revealed that NK cells can also contribute to solid organ transplant rejection. In CD28-deficient mice, NK cells contributed to acute cardiac graft rejection while depletion of NK cells in the absence of CD28-dependent T-cell costimulation prolonged cardiac graft survival [33]. These findings suggest that NK cells can promote T-cell responses during costimulatory blockade. Moreover, NK cells also appear to play a critical role in chronic allograft nephropathy [34]. In a murine model of parental to F_1 cardiac transplants, IFN-γ production by NK cells contributed to cardiac allograft vasculopathy (CAV) [35]. Furthermore, NK cells appear to play a subsidiary role in chronic rejection through the stimulation of Th1 cells, suggesting that the communication of NK cells to players of adaptive immunity may be of critical importance in graft rejection. In addition, recent evidence suggests that NK cells are able to mediate graft rejection in the absence of adaptive immune cells as IL-15-activated NK cells have been able to mediate skin graft rejection (Fig. 3a) [36–40]. Moreover, skin from human α1,2-fucosyltransferase (HTF) transgenic mice grafted onto $RAG^{-/-}$ recipients that lack B and T cells induced rejection that affected 50–95% of the graft at 10–20 days, with the residual graft recovered and survived long-term (>100 days).Rag-1 KO/beige recipients that lack T/B and NK cells did not undergo rejection crisis, supporting a critical role of NK cells in the observed skin graft rejection. (Fig. 3b) [41].

Thus, increasing evidence suggests that NK cells independently or via the communication to adaptive immune responses may contribute to graft rejection. At the same time, a tolerogenic potential of NK cells has been demonstrated. In a murine skin transplant model, graft-derived antigen-presenting cells (APCs) have been eliminated by host NK cells, thereby altering T cell priming, resulting in tolerance induction (Fig. 3c) [42].

Moreover, a number of studies have implicated macrophages as a critical component of transplant rejection, although their role remains not entirely defined. Ischaemia–reperfusion injury (IRI) is inevitably linked to organ transplantation, and macrophages have been closely linked to the pathophysiology of IRI. In lung transplantation, alveolar macrophages (AM) induce tissue injury through the production of a variety of bioactive products such as tumour necrosis factor (TNF)-α, monocyte chemoattractant protein (MCP)-1 and macrophage inflammatory protein (MIP)-2 [43].A recent study indicates that AMs specifically expressed the E3 ubiquitin ligase TRIM29 and that TRIM29 provided a critical role in the maintenance of immunological homoeostasis [44]. Pathophysiological features of

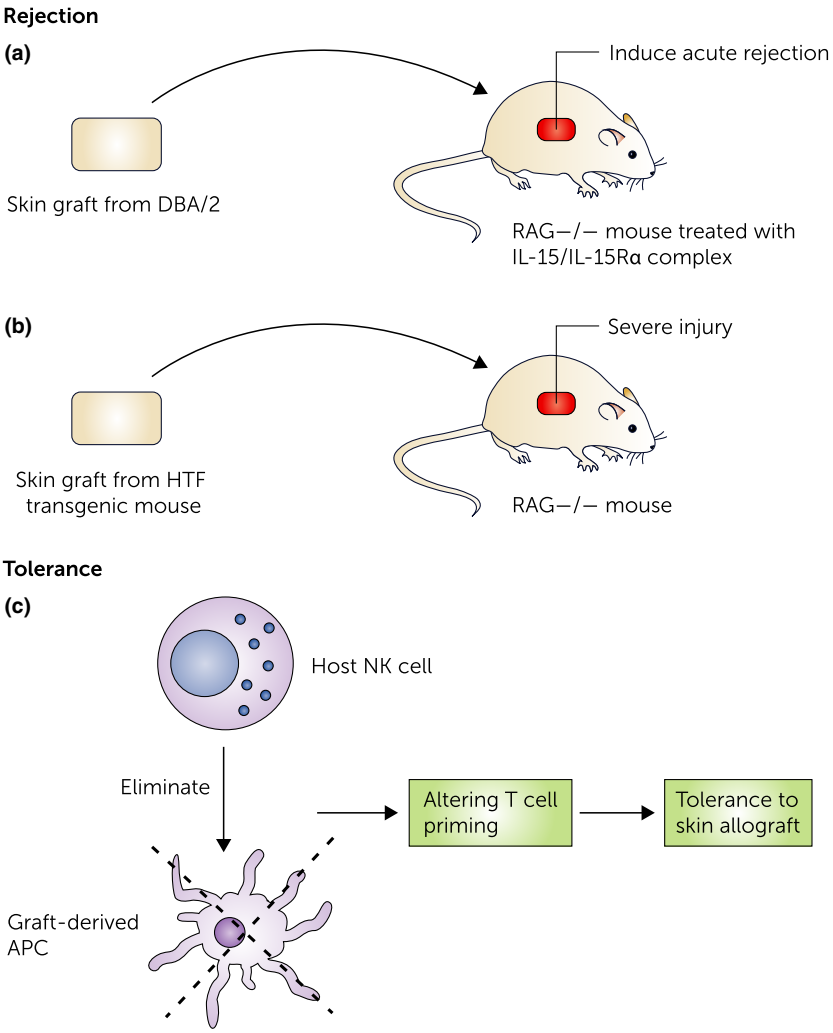

Figure 3 Role of NK cells in alloimmune responses. (a) Skin grafts are rejected in RAG-/- mice when NK cells are activated by the IL-15/IL-15Rα complex. (b) In a mouse skin transplant model, skin allografts from HTF transgenic mice grafted onto RAG-/- mice are injured albeit not completely rejected. (c) In a murine skin transplant model, graft-derived APCs were eliminated by host NK cells, thereby altering T-cell priming, resulting in tolerance induction. APCs, antigen-presenting cells; HTF, human α1,2-fucosyltransferase; Rag, recombination activating gene.

IRI also include the activation of TLRs on macrophages. In cardiac transplantation, macrophages stimulated by high-mobility group box-1 (HMGB-1) through TLR4 activation produced IL-23 that, in turn, induced the generation of IL-17A-producing γδT cells in the heart, demonstrating the significance of an innate-adaptive immunity axis in myocardial IRI [45]. In kidney transplantation, perforin-dependent killing of tubular cells by NK cells is a major pathway [46]. Moreover, expression of CD137 on NK cells and its ligand on tubular epithelial cells seems crucial for the chemokine-mediated recruitment of neutrophils to the site of inflammation [47]. During acute rejection, recipient macrophages are rapidly recruited to the graft [48]. Once macrophages of recipient origin accumulate, the secretion of pro-inflammatory cytokines is initiated. Pro-inflammatory cytokines, including IL-1, IL-6, IL-12, IL-18, IL-23, TNF-α and IFN-γ promote the generation of cytotoxic T cells and induce chemokines such as MCP-1 and macrophage colony-stimulating factor (M-CSF). Moreover, macrophages produce reactive oxygen species (ROS) and reactive nitrogen species (RNS) that augment tissue damage [49].

Concentric arterial narrowing during intimal hyperplasia by smooth muscle-like cells and associated matrix proteins is the principal histopathological finding of chronic vasculopathy [50]. Macrophages have been shown to infiltrate heart allografts, thus contributing to the progress of transplant vasculopathy. Partial depletion of macrophages with intraperitoneal carrageenans (mucopolysaccharides from the cell walls of the red algae) suppressed immune responses via mechanisms that selectively inhibited cytopathic effects, thus improving transplant vasculopathy [51]. Of note, allospecific responses of macrophages have been shown in a recent experimental study with evidence of a more robust response to allografts compared to syngeneic grafts [52]. In this particular study, WT as well

as T cell-, B cell- and innate lymphoid cell-deficient mice receiving allogeneic grafts mounted a persistent differentiation of monocytes into mature DCs. In contrast, syngeneic grafts in the same mice elicited transient and less pronounced differentiation of monocytes, indicating that DAMPS released during ischaemia–reperfusion injury are not sufficient to induce sustained APC maturation to initiate adaptive alloimmune responses. Moreover, in a model in which T-cell recognition is restricted to a single foreign antigen, rejection occurred only if the allogeneic non-self-signal was also sensed by the host's innate immune system. Comparable to NK cells, macrophages appear to play a dual role and have also been linked to tolerance, with regulatory macrophages or Mregs playing an important role in this context [53,54]. Clinically, administration of regulatory macrophages allowed a low-dose tacrolimus monotherapy in living donor kidney transplantation [55].

Conclusion

Recent advances in our knowledge of innate immunity and its key players, NK cells and macrophages, have provided a better understanding of recall capacities in innate immunity. Indeed, the existence of adaptive features of innate immune cells represents a paradigm shift in immunity. Moreover, newly identified innate-like lymphocytes may bridge the missing link between innate and adaptive immunity.

Clearly, adaptive features of innate immunity represent important components of host defences and alloimmunity with broad clinical relevance. Future work will need to delineate ligand specificity and signalling properties to develop targets for treatment.

Authorship

HU participated in the writing of the manuscript. KM, MQ, YN, TH, HA, AEK and SGT participated in the writing of the manuscript, reviewed the manuscript.

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Conflicts of Interest

The authors have declared no conflict of interests.

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