Innate lymphoid cells

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Innate Lymphoid Cells (ILCs): The New Kids on the Block

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Abstract

Purpose of review:

The purpose of this article is to review recent advances in our understanding of innate lymphoid cell function and to speculate on how these cells may become activated and influence the immune response to allogeneic tissues and cells following transplantation.

Recent findings: Innate lymphoid cells encompass several novel cell types whose wide ranging roles in the immune system are only now being uncovered. Through cytokine production, cross-talk with both hematopoietic and non-hematopoietic populations and antigen presentation to T cells, these cells have been shown to be key regulators in maintaining tissue integrity, as well as initiating and then sustaining immune responses.

Summary: It is now clear that innate lymphoid cells markedly contribute to immune responses and tissue repair in a number of disease contexts. Whilst experimental and clinical data on the behaviour of these cells following transplantation is scant, it is highly likely that innate lymphoid cells will perform similar functions in the alloimmune response following transplantation and therefore may be potential therapeutic targets for manipulation to prevent allograft rejection.

Introduction

The term Innate Lymphoid Cells (ILCs) describes a heterogeneous collection of immune cells united by both their differentiation from a common lymphoid progenitor and their lack of a Rag-dependent antigen specific receptor [1]. Recently, ILC subsets have been further defined based on the differential expression of transcription factors and importantly, function. Many of the effector functions ascribed to ILCs have the capacity to significantly impact subsequent adaptive immune responses and as such are likely to modulate alloimmune responses, in addition to the already described roles for these cells in chronic inflammatory disease and immunity to pathogens. Therefore, the aim of this review is to provide an overview of the biology of ILCs and to describe the known functions of these cells that may be pertinent to the immune response to transplants.

Origin, development and characterisation of innate lymphoid cells

ILCs have now been identified throughout the body, and although enriched at mucosal barriers such as the intestine and lung, they have also been described in skin, primary and secondary lymphoid tissue and a growing list of organs such as liver, kidney and pancreas [2,3]. Whilst natural killer (NK) and lymphoid tissue inducer (LTi) cells were described many years previously [4-6] a series of publications in 2010 [7-9] reported several novel immune cell populations, with the ILC nomenclature formally described in 2013 [2]. Under this classification, three groups of ILCs that mirror established groups of effector CD4 T cells were defined based upon their cytokine secretion and transcription factor expression (Figure 1).

Group 1 ILCs are able to produce IFNγ and tumour necrosis factor (TNF), comprising Tbet[+]Eomes^{+} NK cells and a distinct Tbet[+]Eomes[-] ILC1 population. These cells respond to IL-12, IL-15 and IL-18 and promote immunity to viruses, fungi and intracellular bacteria and parasites [10,11, 12[••]].

The group 2 ILCs promote type 2 inflammation, and are defined by their expression of GATA-3 expression and production of the type 2 cytokines IL-4, IL-5, IL-9 and IL-13 in response to IL-2, IL-25, IL-33 and thymic stromal lymphopoietin (TSLP) [7,8,13-15]. They have also been demonstrated to produce amphiregulin, a member of the epidermal growth factor family, which is important for tissue remodelling and repair [16]. Recently the ILC2 compartment was further divided into IL-25 responsive inflammatory ILC2 (iILC2), which lack expression of ST2 (IL-33R), and ST2^{+} natural ILC2 (nILC2) that respond principally to IL-33 [17[••]].

The third group of ILCs (ILC3) express the retinoic acid orphan receptor (ROR) splice variant RORγt and produce IL-22, Csf2 and to a lesser extent IL-17 [18, 19[••]]. This group includes LTi cells in the embryo, their phenotypically-equivalent (LTi-like) cells in the adult and distinct populations described principally in the small and large intestine, which differ in their expression of surface markers such as NK cell receptors (NCR) and additional production of IFNγ [9,20]. Furthermore, there is clear evidence that some ILC3s can down regulate RORγt expression and develop an ILC1 phenotype. ILC3s respond to cytokines such as IL-1β and IL-23. These cells are also clearly influenced by the presence of commensal bacteria, likely through indirect stimulation with the cytokines above, but perhaps also direct recognition. A basic description of ILC groups is summarised in Figure 1. This simple framework has

facilitated enormous advances in understanding the development and differentiation of ILC populations, adding layers of complexity to this basic description.

Klose et al. [12$^{••}$] recently defined the common progenitor to all helper-like ILCs (CHILP), a lineage$^-$ Id2$^+$ IL-7Rα^+ CD25$^-$ $\alpha_4\beta_7^+$ progenitor population in bone marrow and fetal liver able to give rise to all groups of ILC, with the exception of conventional NK cells, which are distinct from helper ILCs by virtue of their cytotoxic activity. Downstream of the CHILP, and distinguished by expression of transcription factor pro-myeloid leukaemia zinc finger (PLZF), is a progenitor unable to develop into either conventional NK cells or LTi cells, but able to form the remaining ILC populations [21$^{••}$]. Therefore current understanding indicates a succession of several ILC progenitor populations with progressively limited precursor potential. It is now also clear that all helper ILC populations require GATA-3 for their development, not just ILC2 [22$^•$,23$^•$]. Given several excellent reviews on ILC differentiation [3,24,25], here we will focus on recent advances in our understanding of ILC function, the potential roles of these cell in immunity, and how these cells may influence innate and adaptive immune responses to solid organ transplants.

ILCs regulate barrier integrity and tissue formation/repair

The prototypic ILC, the LTi cell was first identified for its role in the formation of lymph nodes (LNs) and Peyer's patches, a developmental process restricted to the embryo and neonate [6]. At this time, LTi cell provision of (LT$\alpha_1\beta_2$) to specialised stromal organiser cells that express LTβR, results in their production of the homeostatic chemokines CCL19, CCL21 and CXCL13, recruiting lymphocytes to the anlagen [26] (Figure 2A). After birth, LTi cells are

further required for the generation of isolated lymphoid follicles within the intestine. Interestingly, within adult secondary lymphoid tissue, LTi-like cells persist in the same microenvironments as stromal cells that phenotypically resemble the stromal organiser population in the embryo, suggesting continued interactions between these populations might be involved in tissue homeostasis [27,28]. ILC3s have been shown to aid tissue repair in the spleen following viral infection [29], indicating a specific role for these cells following tissue damage (Figure 2A). Whilst there is no clear consensus on whether ILC3 are involved in tertiary lymphoid tissue (TLT) formation [30], ILC3s may facilitate the generation of TLT which is pertinent to transplantation as TLT has been reported to be present in many allografts undergoing chronic rejection [31,32]. However, as yet studies have not looked for the presence of ILCs in TLT in transplants or assessed whether they contribute to the formation of such structures.

A major function of ILCs is the maintenance of epithelial integrity and its repair following insult (Figure 2A) [16,33,34]. In the intestine, IL-22 is necessary for epithelial integrity to bacterial infection [35] and ILC3s, the dominant ILC population in this tissue, are a key source of this cytokine [34]. In the absence of ILC3s, there is impaired containment of commensal bacteria within this site and dissemination of specific species [33]. It was recently identified that production of IL-22 by ILC3s, in addition to lymphotoxin $\alpha_1\beta_2$ signals, induces intestinal epithelial Fut2 expression and fucosylation of these epithelial cells, provides a substrate for commensal bacteria. This in turn can inhibit colonisation by pathogens such as *Salmonella typhimurium* [36[•]], underlining the importance of ILC3s in normal intestinal homeostasis (Figure 2B).

Within the lung, IL-22 derived from ILC3s also serves a protective role limiting inflammation in allergic disease and also following Streptococcus pneumoniae infection [37,38]. It was recently shown that in obesity associated asthma there was dysregulation of the normal ILC populations in the lung with IL-1β-driven expansion of IL-17A producing ILC3s causing airway hyper-reactivity [39]. It is not only ILC3s that contribute to tissue integrity and within the lung. Amphiregulin, produced by ILC2s, was shown to restore the loss of airway epithelial integrity observed following depletion of ILCs [16], indicating an important role for ILC2s in preserving lung epithelium. [40]

Interestingly, a role for ILC3s in maintaining barrier integrity has been described in allogeneic bone-marrow/haematopoietic stem cell (BM/HSC) transplantation where the presence of activated, donor-derived NCR[+] ILC3s in the peripheral blood correlated with decreased incidence of graft versus host disease (GVHD) in patients receiving an allogeniec HSC transplant [41[•]]. Furthermore, Hannash et al found that recipient ILC3s produce IL-22 which promotes gut epithelial barrier integrity and limits GVHD in a mouse model [42]. This is clearly relevant to intestinal as well as HSC transplantation but whether ILCs present in or homing to other organs initiate the same repair mechanisms after solid organ transplantation remains to be seen.

ILC crosstalk with other innate cells

Cells of the immune system do not exist in isolation and recent studies have shed light on the interactions of ILCs with other innate cell populations. Recent evidence indicates that ILC signals to antigen presenting cells (APC) can modulate their behaviour, thus indirectly contributing to the initiation or establishment of an immune response (Figure 2B). For example, colonic CX_3CR1^+ mononuclear phagocytes (MNPs), such as macrophages and DC, cluster with ILC3s, likely within isolated lymphoid follicles, and produce IL-23 and IL-1β in response to bacteria, driving ILC3 production of IL-22 [43]. Production of IL-1β by MNPs also stimulates ILC3 production of Csf2, which feeds back to the DC and macrophages enhancing their support of intestinal Tregs [19••]. Distinct from such interactions within isolated lymphoid follicles, $NKp46^+$ ILC3 require CXCR6 to interact with CXCL16 expressing $CD11b^+CD103^-$ intestinal DC within the lamina propria. These DC also produce IL-23 and the crosstalk mediated by CXCR6:CXCL16 was required for IL-22 mediated protection from *C. rodentium* infection [44]. Given the close interplay between ILC and different APC populations in the intestine, it seems likely that further examples of crosstalk between these populations in maintaining intestinal homeostasis will be discovered.

Within visceral adipose tissue ILC2 are important for maintaining eosinophils and alternatively activated macrophages (AAM) via production type 2 cytokines [45]. ILC2 support for AAM is likely to exist at other sites and Huang and colleagues recently found that AAM were induced by IL-25 activated ILC2 and that the induction of such cells afforded protection in a model of renal ischemia reperfusion injury [46].

ILCs as antigen presenting cells

A major recent advance in our understanding of ILC function emerged from the demonstration that both ILC2 and ILC3 populations are able to process and present antigen in the context of MHCII, thus establishing a mechanism for directly interacting with CD4 T cells (Figure 2C) [47, 48**]. What are the consequences of such interactions? Sophisticated mouse models that specifically target ILC2s demonstrated a role in the development of robust Th2 responses [48**]. ILC2s clearly potentiate the Th2 response, since expulsion of the parasite *N. brasiliensis* is impaired when ILC2s lacked MHCII [48**]. Both human and murine ILC2 isolated from secondary lymphoid tissue express intermediate levels of MHCII, intermediate levels of CD80, but little CD86 [48**]. Consistent with this, in vitro these cells can drive naïve CD4 T cell proliferation [48-50], however, direct evidence that ILC2 drive naïve CD4^{+} T cell proliferation in vivo is currently lacking. ILC2s may signal to CD4^{+} T cells via other costimulatory molecules such as OX40L [50]. Importantly, these are reciprocal interactions beneficial to both T cell and ILC2, with IL-2 now known to enhance ILC2 cytokine production [48**] (Figure 2C).

Amongst the ILC3 group, the LTi-like population are also able to process and present antigen in the context of MHCII but lack expression of CD80, CD86 and CD40 and were unable to drive naïve CD4^{+} T cell proliferation in vitro [47]. Strikingly, genetic deletion of MHCII on ILC3 using RORγt cre x fl H2-Ab1[fl] mice resulted in dysregulated CD4^{+} T cell responses to commensal bacteria in vivo, indicating that ILC3, rather than potentiating T cell responses, have a regulatory role although the mechanism remains to be defined [47] (Figure 2C). Whether this regulation of the T cell response occurs within the intestine or the draining mesenteric LN tissue is unclear, but it is noteworthy that LTi-like ILC3s are located only

within the interfollicular spaces of the mesenteric LN (mLN) [51], a site through which activated CD4^{+} T cells traffic.

The recent comprehensive analysis of ILC transcriptomes revealed neuropilin-1, known to enhance interactions between Treg and DC [52], to be expressed only on LTi-like ILC3s [•53]. Since ILC3s are able to traffic from the intestine to the mLN [51], an attractive hypothesis is that these cells sample antigen from the intestine, then travel to the draining LNs where they regulate CD4^{+} T cell responses [51].

Our current understanding, particularly in light of their costimulatory molecule profile, indicates that ILCs are atypical APCs in T cell responses, rather than direct replacements of professional APCs such as the dendritic cell [54]. Further understanding of exactly which types of CD4^{+} T cell interact with ILCs and when, is essential to better define the direct role of these cells in CD4^{+} T cell responses. Hepworth et al., were unable to detect any effects on Tregs in RORγt cre x fl H2-Ab1[fl] mice [47], however definitive studies require antigen specific populations to be studied. LTi-like cells support memory CD4^{+} T cells in vivo but, the mechanisms controlling this have not been defined [28].

 Understanding what controls ILC expression of MHCII and costimulatory molecules may shed light on the possible mechanisms by which the outcome of T cell:ILC interactions are determined. It is known that ILC expression of MHCII, and in the case of ILC2, the costimulatory molecules CD80 and CD86 is dependent upon the location from which they

are isolated [47,48]. Intriguingly, a separate study using RORγt cre x fl H2-Ab1[fl] mice indicated a role for splenic ILC3 in enhancing CD4^{+} T cell numbers [55] suggesting the location-specific differences observed in ILC phenotype may impart different effects on T cell responses.

ILC modification of adaptive immune responses through soluble molecule production

T cells activated in a given cytokine milieu preferentially differentiate into functionally distinct Th1, Th2 or Th17 T helper cell subsets. Given that ILCs rapidly secrete many cytokines known to direct such T cell differentiation (i.e. ILC1 produced IFNγ, ILC2 produced IL-4 and IL-23 produced by ILC3s) one might suspect that ILCs influence adaptive immunity through the provision of cytokine which in turn would be dictated by the local balance of ILC subsets and signals that differentially activate ILC subsets. Currently there is little evidence to support this. However, in type 2 immune responses, IL-13 production by ILC2 is important for DC activation and trafficking to the draining LN, where the CD4^{+} T cell response is initiated [56•]. Interestingly, ILC2s can also produce amphiregulin (in response to the alarmin, IL-33) which in addition to well characterised functions such as tissue repair and homeostasis has been found to enhance the suppressive capacity of Treg upon binding the epidermal growth factor receptor [57,58]. Therefore, soluble factors from ILCs may positively or negatively impact adaptive immune responses (Figure 2B).

Conclusion

ILCs have been shown to significantly impact both innate and adaptive immunity via the secretion of cytokines and other soluble molecules as well as through direct antigen presentation to T cells. Despite the lack of direct evidence, these observations suggest that ILCs may also be active following transplantation. However, further studies are clearly needed to determine the activation status, transplant/lymphoid tissue trafficking and effector function of these cells after transplantation before therapeutic strategies can be employed to manipulate these cells to minimise ischemia reperfusion injury and rejection.

Key points

- ILCs are a novel immune cell family with a broad range of functions.

- The effects of ILCs on adaptive immune responses are mediated through a range of direct and indirect mechanisms.

- As APCs, ILCs can directly control CD4$^+$ T cell responses.

- ILCs may enhance or suppress adaptive immunity.

- ILCs have the capacity to influence adaptive and innate responses to transplanted organs and cells and as such may be therapeutically targeted to attenuate ischemia reperfusion injury and rejection and control the repair of transplanted tissue.

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FIGURE 1. Schematic showing different ILC subsets developing from the common lymphoid progenitor. For each group, the signals to which they respond are shown alongside the molecules secreted. Areg amphiregulin; CHILP, common progenitor to all helper-like ILCs; CLP, common lymphocyte progenitor; PLZF, promyeloid leukaemia zinc finger; TSLP, thymic stromal lymphopoietin.

FIGURE 2. Schematic showing known functions of ILC2 and ILC3 pertinent to transplantation.

A) Direct interactions of surface receptors. ILC3 provision of lymphotoxin $\alpha_1\beta_2$ in the development of lymph nodes and repair of splenic stroma. B) Production of soluble molecules by ILCs. ILC3 production of IL-22 enhances intestinal epithelium integrity; ILC2 production of IL-13 enhancing DC migration or amphiregulin suppressing regulatory T cells. C) ILC Presentation of antigen in MHCII. ILC3 regulation of CD4^{+} T cell responses to commensal bacteria; ILC2 enhancement of Type 2 responses. Areg amphiregulin; IEC, intestinal epithelial cell; LT, lymphotoxin; MNP, mononuclear phagocyte; NRP-1, neuropilin-1.
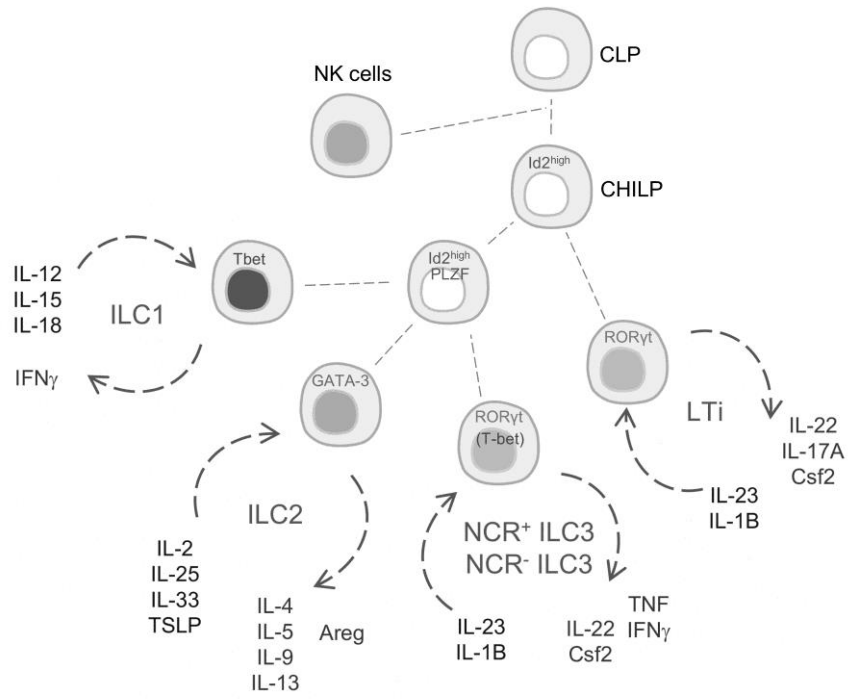
FIGURE 1.

FIGURE 2.