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Review

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Review

Protective and pathogenic functions of innate lymphoid cells in transplantation

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Summary

Innate lymphoid cells (ILCs) are a family of lymphocytes with essential roles in tissue homeostasis and immunity. Along with other tissue-resident immune populations, distinct subsets of ILCs have important roles in either promoting or inhibiting immune tolerance in a variety of contexts, including cancer and autoimmunity. In solid organ and hematopoietic stem cell transplantation, both donor and recipient-derived ILCs could contribute to immune tolerance or rejection, yet understanding of protective or pathogenic functions are only beginning to emerge. In addition to roles in directing or regulating immune responses, ILCs interface with parenchymal cells to support tissue homeostasis and even regeneration. Whether specific ILCs are tissue-protective or enhance ischemia reperfusion injury or fibrosis is of particular interest to the field of transplantation, beyond any roles in limiting or promoting allograft rejection or graft-versus host disease. Within this review, we discuss the current understanding of ILCs functions in promoting immune tolerance and tissue repair at homeostasis and in the context of transplantation and highlight where targeting or harnessing ILCs could have applications in novel transplant therapies.

Keywords: innate lymphoid cells, natural killer cells, immune tolerance, immune regulation, transplantation, graft-versus-host disease, hematopoietic stem cell transplant, rejection, ischemia reperfusion injury

Abbreviations: ACR: acute cellular rejection; APCs: antigen presenting cell; ABMR: antibody mediated rejection; ADCC: antibody-dependent cell-mediated cytotoxicity; BAL: bronchoalveolar lavage; DC: dendritic cell; EOMES: eomesodermin; G-CSF: granulocyte colony stimulating factor; GM-CSF: granulocyte macrophage colony stimulating factor; GVHD: graft versus host disease; GVL: graft versus leukemia; HLA: human leukocyte antigen; HSCT: hematopoietic stem cell transplant; IFN-γ: interferon-gamma; IL: interleukin; ILC: innate lymphoid cell; ILC1: group 1 innate lymphoid cell; ILC2: group 2 innate lymphoid cell; ILC2: group 3 innate lymphoid cell; ILCP: innate lymphoid cell precursor; IRI: ischemia reperfusion injury; KIR: killer cell immunoglobulin-like receptor; LTi: lymphoid tissue inducer; MDSC: myeloid derived suppressor cell; MHC: major histocompatibility complex; NK cell: natural killer cell; NCR: natural cytotoxicity receptor; ROS: reactive oxygen species; scRNAseq: single cell RNA sequencing; TEC: tubular epithelial cells; TNF-α: tumour necrosis factor alpha; Tregs: CD4 regulatory T cell.

Introduction

Innate lymphoid cells (ILCs) are a family of innate lymphocytes with important roles in tissue homeostasis. Through their rapid production of cytokines and capacity to interface with both immune and non-immune cells, ILCs modulate and direct immune responses involved in host defense, tissue repair, and immune tolerance [1–5]. Differentiated ILCs and ILC precursors in circulation can infiltrate into tissues and develop tissue-adapted functions, a process termed "tissue-poiesis." [6, 7] Once ILCs take up residency within an organ, they can serve as tissue sentinels, modulating local immunity [8–11], and participating in a broad range of biological processes such as neuronal regulation, epithelial remodeling, adipogenesis, and circadian rhythms [12–15]. While early parabiotic mouse studies of ILCs supported tissue ILCs are "resident" and do not traffic between organs [16], recent studies have observed some ILCs can migrate between the intestines, lung, and liver [17–19], supporting that specific signals promote trafficking of a subset of ILCs to elsewhere in the body. However, features of ILCs that traffic to other locations and signals which direct this are only beginning to be elucidated.

The ILC family includes both cytotoxic and non-cytotoxic or "helper" subsets(Figure 1). Natural killer(NK) cells have important roles in eliminating virally infected cells and tumor cells through their ability to discriminate between self and non-self. This is accomplished primarily via recognition of major histocompatibility complex (MHC) molecules; cells that lack self-MHC molecules due to viral or tumor cell downregulation, or cells of allogeneic origin, are eliminated by NK cells via cytotoxic mechanisms mediated by granzymes and perforin. NK cells also produce pro-inflammatory cytokines interferon-gamma (IFN-γ) and tumor necrosis factor alpha (TNF-α), which contribute to additional pro-inflammatory processes. In humans, NK cells are further classified as $CD56^{dim}CD16^{+}$NK cells, which exhibit potent cytotoxic

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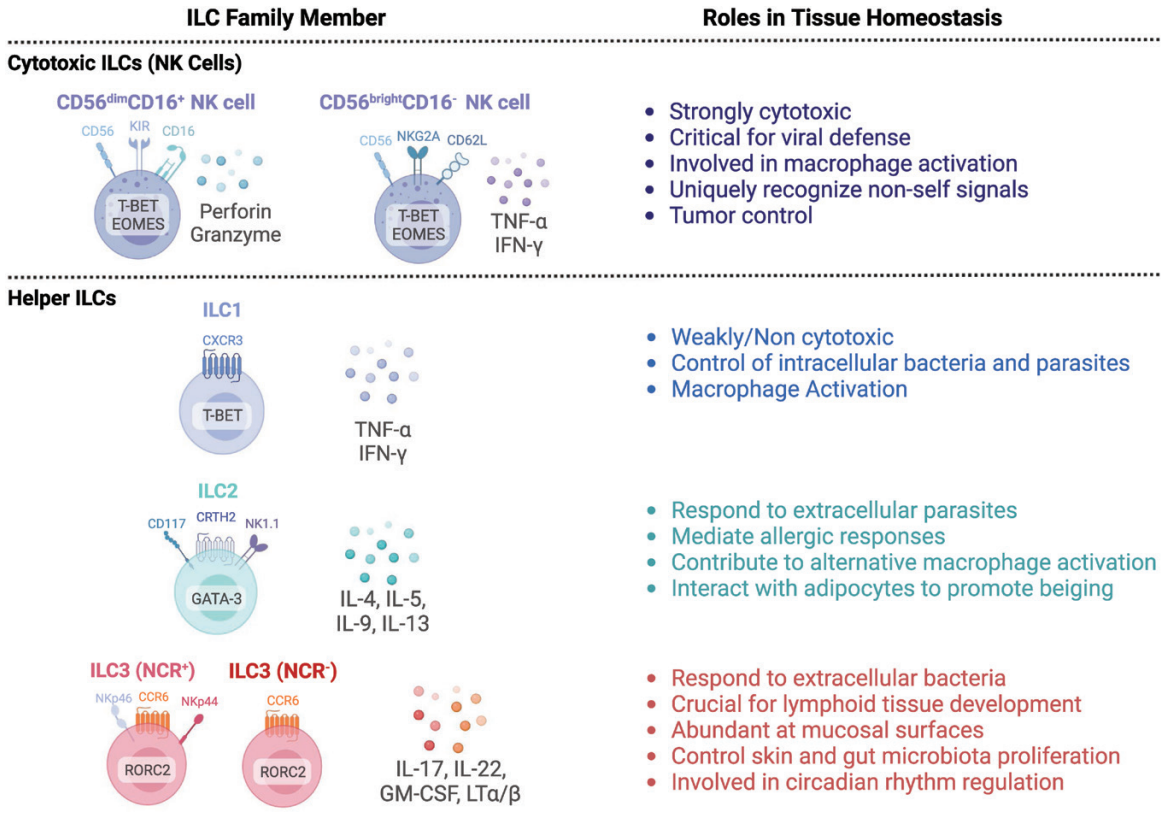

Figure 1. The innate lymphoid cell family. ILCs are divided by cytotoxic (top) and non-cytotoxic (bottom) subsets. Cytotoxic ILCs include natural killer (NK) cells, which are subdivided into two major subsets based on expression of CD56 and CD16. Helper ILCs include ILC1s, ILC2s, and ILC3s, with ILC3s being further divided based on those that express the natural cytotoxicity receptor (NCR). Human ILC defining surface markers, cytokines, and transcription factors indicated, along with their established roles in host defense and tissue homeostasis. Created with Biorender.com.

potential, and CD56^{bright}CD16^{-}NK cells which produce high levels of NK cell-associated cytokines [20–23]. Helper ILCs are divided into groups based on cytokine and transcription factor expression. Group 1 ILCs (ILC1s) produce IFN-γ [24] and protect against viral infections, although ILC1s are generally described as lacking cytotoxic potential and do not express molecules such as killer cell immunoglobulin-like receptors (KIRs) important for distinguishing self and non-self, or the transcription factor Eomesodermin (*EOMES*). Group 2 ILCs (ILC2s) produce interleukin (IL)-4, IL-5, IL-13, and IL-9 to contribute to parasite and helminth immunity, and also maintain tissue homeostasis by interfacing with parenchymal cells to promote epithelial repair in tissues such as the intestine, lung, and skin(Fig. 2) [25–27]. Group 3 ILCs (ILC3s) produce IL-22, IL-17, and granulocyte-macrophage-colony-stimulating-factor(GM-CSF), and respond to extracellular bacteria. Similar to ILC2s, ILC3s are important for tissue homeostasis, possessing roles in skin repair and control of intestinal inflammation [28–32](Fig. 2).

While ILCs have important roles in tissue homeostasis [1], aberrant ILC responses can promote tissue injury [33–39]. For example, ILC2s can recruit eosinophils that exacerbate lung and muscle injury [33–35], and through IL-22 and IL-17A, ILC3s can contribute to airway inflammation [36–38]. Tissue signals have key roles in directing these protective or pathogenic functions of ILCs. For example, IL-33 signaling is critical in facilitating ILC2 activation and production of amphiregulin to promote airway epithelia repair in mice [25], while IL-25 signaling can promote IL-5 production from mouse ILC2s, resulting in eosinophilia that contributes to lung inflammation [40, 41]. Thus ILC-tissue interactions are key for maintaining tissue homeostasis.

In addition to canonical ILCs, recent studies have identified populations of ILCs with immunosuppressive capabilities in contexts such as cancer, allergy, and autoimmunity [42–47]. These regulatory ILCs include IL-10 producing ILC2s, NK-like regulatory ILCs, and ID3^{+} regulatory ILCs [48]. Understanding, however, of their ontogeny and contexts in which they arise is not well characterized, however, most data currently supports they are canonical ILCs that acquire immunoregulatory functions in response to microenvironment triggers.

Despite wide-spread interest in ILCs, their role in solid organ transplantation and other allogeneic contexts is only beginning to be elucidated. Key questions include whether they contribute to tolerance or rejection, and how donor and infiltrating recipient-derived ILCs interface with other immune and non-immune cells to coordinate responses following transplant. Herein we discuss the known functions of ILCs in tissues and examine the current understanding of ILCs protective or pathogenic functions in allogeneic contexts. We also explore potential therapeutic applications of ILCs for transplantation and identify areas of research needed to evaluate this potential.

Challenges limiting success of transplantation

Transplantation is widely used to treat end-stage organ disease. During transplantation, the organ can suffer ischemia

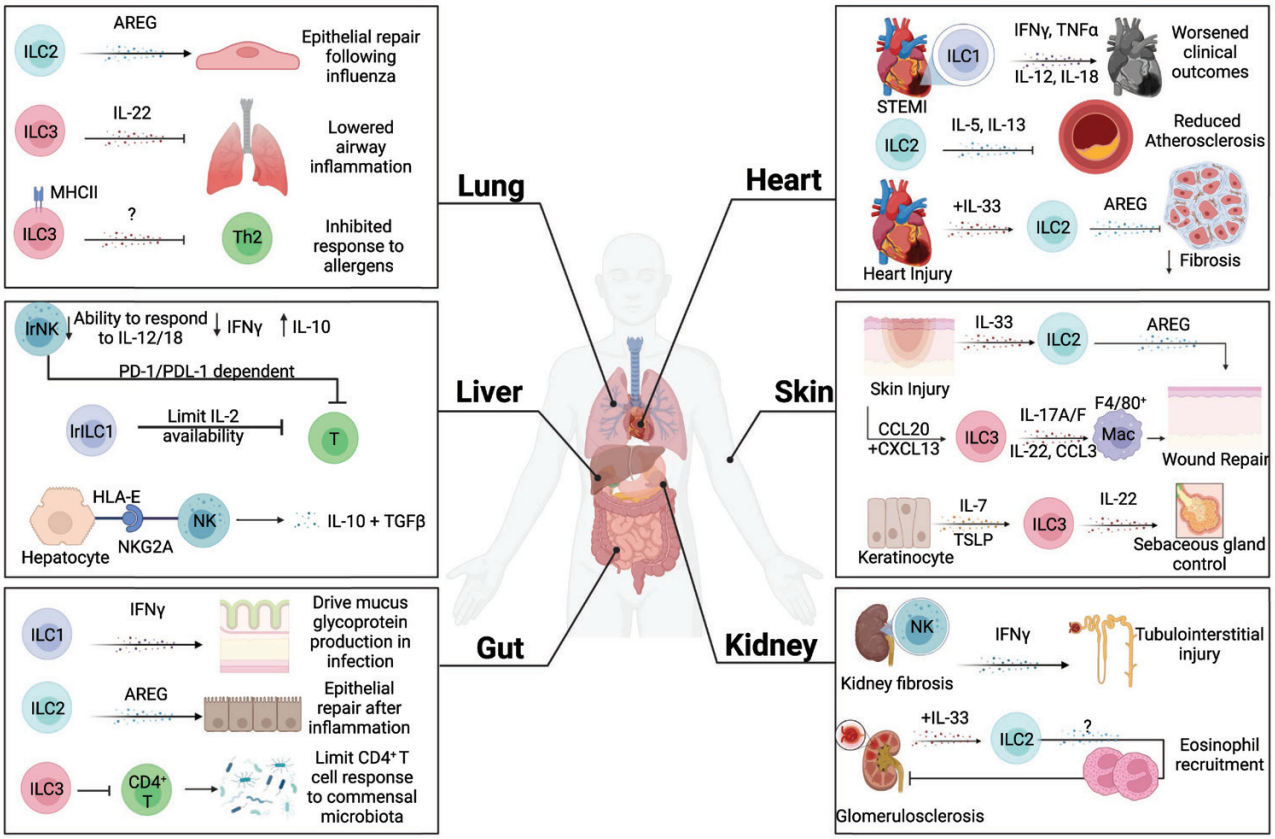

Figure 2. ILC functions in promoting or inhibiting tissue tolerance. ILCs can exhibit organ-adapted functions and can differ in having protective or pathogenic functions, depending on the tissue. (Lung): Within the lung, ILC2s are required to maintain airway epithelial integrity following influenza infection through production of amphiregulin (AREG). Lung ILC3s expressing MHC class II can also limit Th2 cell responses to allergen and ILC3-derived IL-22 reduces inflammation following allergen challenge. (Liver): Liver-resident NK cells (lrNK) are characterized by lower responsiveness to IL-12 and IL-18, reduced production of IFN-g, and the ability to produce IL-10. They can also inhibit T-cell responses via a PD-1/PDL-1 axis. ILC1s within the liver can also promote immune tolerance by limiting IL-2 availability, thereby inhibiting $CD8^+$ T-cell responses. Circulating NK cells were also shown to produce IL-10 and TGF-b following NKG2A interactions with HLA-E on hepatocytes. (Gut): ILC1s are essential for restoring normal mucus glycoprotein production following Salmonella infection. In a murine model of intestinal damage, ILC2s limited inflammation and promoted repair in an amphiregulin (AREG)-dependent mechanism. ILC3s maintain immune homeostasis by limiting intestinal $CD4^+$ T-cell responses to commensal bacteria. (Heart): In acute ST-segment elevation myocardial infarction (STEMI), ILC1s were increased in circulation, and their presence correlated with adverse clinical outcomes that was attributed to ILC1 production of IL-12, IL-18, TNF-a, and IFN-g. In a murine high fat diet model, ILC2s protected from atherosclerosis through IL-5 and IL-13. IL-33 expanded ILC2s were also capable of reducing cardiac fibrosis via amphiregulin (AREG) effects. (Skin): ILC2s are recruited to the site of skin injury via IL-33 and promote repair through amphiregulin (AREG). ILC3s can be recruited to the site of injury via CCL20 and CXCL13, produce IL-17, IL-22, and CCL3 to directly support wound repair and recruitment of reparative macrophages. ILC3s also adopt tissue residency in the skin by IL-7 and TSLP released by keratinocytes, and can then negatively regulate sebaceous gland to control the skin microbiome. (Kidney): NK cells are enriched in fibrotic kidneys and produce the majority of IFN-g, contributing to inflammation and tubulointerstitial injury. In a mouse model of glomerulosclerosis, IL-33 expanded ILC2s and recruited eosinophils to protect from glomerulosclerosis. Created with Biorender.com.

reperfusion injury(IRI). This involves hypoxic damage that occurs during organ retrieval, which can lead to cell death and release of pro-inflammatory cytokines [49]. Additional damage occurs upon restoration of oxygen to the organ, leading to the generation of reactive oxygen species(ROS) that promote expression of cellular adhesion molecules by endothelial cells. This combined with initial hypoxic damage leads to immune infiltration and inflammation [50]. Several immune populations participate in IRI; neutrophils exacerbate damage through the further production of ROS and pro-inflammatory cytokines TNF-α, IL-6, and IL-8 [51]. Damaged and necrotic cells release large amounts of danger-associated molecular patterns (DAMPs) and activate the complement cascades, both of which activate macrophages leading to tissue damage. T cells are also involved in IRI-induced pathology, as T-cell deficient mice experience reduced IRI [52, 53], with $CD4^+$ T helper (Th) 1 cells having harmful functions and $CD4^+$ Th2 cells having protective roles in IRI [54]. NK cells have also been linked to promoting IRI damage, while subsets of ILCs are suggested to have protective functions. Therefore, complex cellular circuits, involving both resident immune cells and infiltrating immune cells from the recipient can contribute to IRI.

Rejection of transplanted organs remains a major challenge for the success of transplantation. Alloantigens can be recognized through direct or indirect pathways; the direct pathway involves recognizing alloantigens presented on donor antigen presenting cells (APCs), while indirect recognition involves the presentation of alloantigens by recipient's APCs. Both pathways can activate downstream immune mechanisms that lead to graft rejection [55]. Cellular rejection is highly dependent on T-cell responses, which can be directed against

non-self MHC molecules or against alloantigens presented by APCs. In addition to cellular rejection, antibody-mediated rejection (ABMR)—or humoral rejection—is mediated by antibody responses against antigens found on the graft, particularly endothelial cells. ABMR leads to vascular damage through complement activation and subsequent macrophage attack, as well as NK cell killing through antibody-dependent cell-mediated cytotoxicity (ADCC). To prevent rejection, optimized human leukocyte antigen (HLA) matching and immunosuppressive regimens aim to limit harmful immune responses. However, specialized populations of immunosuppressive immune cells, such as regulatory T cells (Tregs) also serve to inhibit pathogenic immune cells. Regulatory T cells can suppress T cells, B cells, and APCs, through a variety of mechanisms including secretion of anti-inflammatory cytokines (i. e. IL-10 and TGF-β1), depletion of extracellular ATP through CD39, and sequestering of IL-2 necessary for effector T-cell proliferation [56]. The ability of Tregs to promote tolerance of allogeneic transplants has led to widespread interest in harnessing Tregs as a tolerogenic cell therapy [57–59].

In addition to solid organ transplant, allogeneic hematopoietic stem cell transplant (HSCT) is another common allogeneic therapy. HSCT is used to treat a wide range of immunological disorders and hematological malignancies. The success of HSCT is driven by the ability of donor-derived T cells and NK cells to attack leukemic cells, termed the graft-versus-leukemia effect (GVL). Despite the potential curative effect of alloHSCT, the success of this therapy is limited by the high proportion of individuals that develop graft-versus-host disease(GVHD), where donor T and NK cells attack host tissue [60]. The acute form of GVHD (aGVHD) generally affects the skin, gastrointestinal tract, and liver, while chronic GVHD (cGVHD) affects multiple organs [61]. Despite improvements in donor matching, cell sources, and immunosuppression, ~40% of patients receiving matched-related donor transplants develop aGVHD, with higher rates in other HSCT transplant types [62]. While inflammatory immune interactions between APCs and T cells drive aGVHD initiation [63], important tissue-protective and immunoregulatory roles have been reported for regulatory T cells, myeloid-derived suppressor cells (MDSCs) and ILCs.

Functions of ILCs in allogeneic hematopoietic stem cell transplantation

Several studies have linked NK cells to protection from GVHD, while also still maintaining the GVL response. Early findings demonstrated that a high infused dose of NK cells, rapid reconstitution of NK cells, or a high NK cell:$CD8^+$ T-cell ratio all correlated with protection from GVHD development without impairing GVL responses [64–68]. In haplo-mismatched HSCT, recipients receiving KIR ligand incompatible grafts were completely protected from both leukemia relapse and aGVHD [69]. Mouse models have provided insights into the molecules underlying NK cells protective functions following HSCT. Using a MHC mismatched mouse model, pre-infusion with alloreactive donor NK cells completely prevented GVHD development and resulted in a marked reduction in $CD11c^+$ APCs in the bone marrow, spleen, and gut (Fig. 3A) [69]. This ablation of APCs appears to require natural cytotoxicity receptor NKp46, as NKp46-deficient mice had more severe GVHD, as did mice given NK1.1 depleted grafts [70]. Supporting *in vivo* studies, NK cells from mice and HSCT recipients could limit T-cell IFN-γ production and directly lyse activated T cells *in vitro* in an NKG2D-dependent mechanism [71, 72] (Fig. 3A). Additional studies have indicated that reconstitution of specifically $CD56^{bright}$ NK cells reduced the incidence of GVHD [73–75]. Decreased proportions of $CD56^{bright}$ NK cells were observed in HSCT recipients with aGVHD compared to those without [73]. Additionally, when patients were divided into groups based on the number of circulating $CD56^{bright}$ NK cells, patients in the "high" group had an overall survival 2-years post-HSCT of 92.9% compared to only 66.7% and 42.9% in the "middle" and "low" groups, respectively [73].

Helper ILC reconstitution is important for establishment of tissue-specific adaptive immunity post-HSCT, whereas ILCs may serve redundant roles in systemic immunity, in line with mouse studies that observe a key role of ILC2 in regulating local but not systemic CD4 T-cell responses [8–11]. However, increased circulating donor-derived ILC2s and ILC3s in HSCT recipients corresponded with decreased aGVHD incidence [76–78]. Munneke *et al.* longitudinally sampled HSCT recipients during conditioning therapy and post-transplant, and reported circulating helper ILCs were diminished after chemotherapy, and ILC1s, ILC2s, and natural cytotoxicity receptor $(NCR)^-$ ILC3s did not recover 12 weeks post-transplant [76]. Phenotyping revealed ILCs in HSCT recipients protected from aGVHD had elevated expression of CD69 and $CD69^{high}$ ILCs had increased expression of gut homing marker α4β7, which correlated with reduced intestinal GVHD [76]. Separately, fewer circulating $NKp44^+$, $CD25^+$ or $CCR6^+$ ILC precursors(ILCPs) were associated with cGVHD development, while fewer ILC2s and ILCPs with aGVHD [77]. Intriguingly, a high proportion of ILCs in granulocyte-colony-stimulating-factor (G-CSF) mobilized grafts correlated with better ILC recovery post-transplant and lower aGVHD incidence, indicating ILCs in HSC grafts may help restore the ILC compartment [78].

In murine studies, ILC3s were shown to protect gut tissues from GVHD pathology. Hanash *et al.* demonstrated IL-22 produced by recipient-derived intestinal ILC3s protected from development of GVHD in an MHC-mismatch model [79]. $IL\text{-}22^{-/-}$ mice had increased epithelial damage, more severe GVHD and lost $IL\text{-}22R^+$ intestinal stem cells, supporting that ILC3-derived IL-22 protects intestinal stem cells and decreases intestinal damage(Fig. 3A) [79]. Separately, intestinal $CD39^+CD73^+$ILC3s were decreased in GVHD patients compared to non-inflamed tissue from individuals with IBD, and serum adenosine was lower in GVHD patients relative to healthy controls [80]. To support a direct role for ILC3 conversion of ATP into immunosuppressive adenosine underlying these patient observations, human $CD39^+CD73^+$ILC3s from healthy donor tonsils suppressed T-cell proliferation *in vitro* in an adenosine-dependent manner(Fig. 3A) [80].

Emerging evidence supports potential therapeutic applications of ILCs in HSCT. Infusion of *in vitro* expanded donor or third-party murine ILC2s improved mouse survival, and reduced symptoms of GVHD [81, 82]. Infused ILC2s trafficked to the gastrointestinal tract, where a reduction in donor $IFN\text{-}\gamma^+$ $CD4^+$ and $CD8^+$ T cells was observed, as well as an increase in donor myeloid derived suppressor cells (MDSCs) [82]. When MDSCs were ablated using anti-GR-1 or $IL\text{-}13^{-/-}$ ILC2s were transferred that were unable to recruit MDSCs, the benefits of ILC2 infusion were ameliorated [82]. Interestingly, ILC2-derived amphiregulin improved intestinal barrier function,

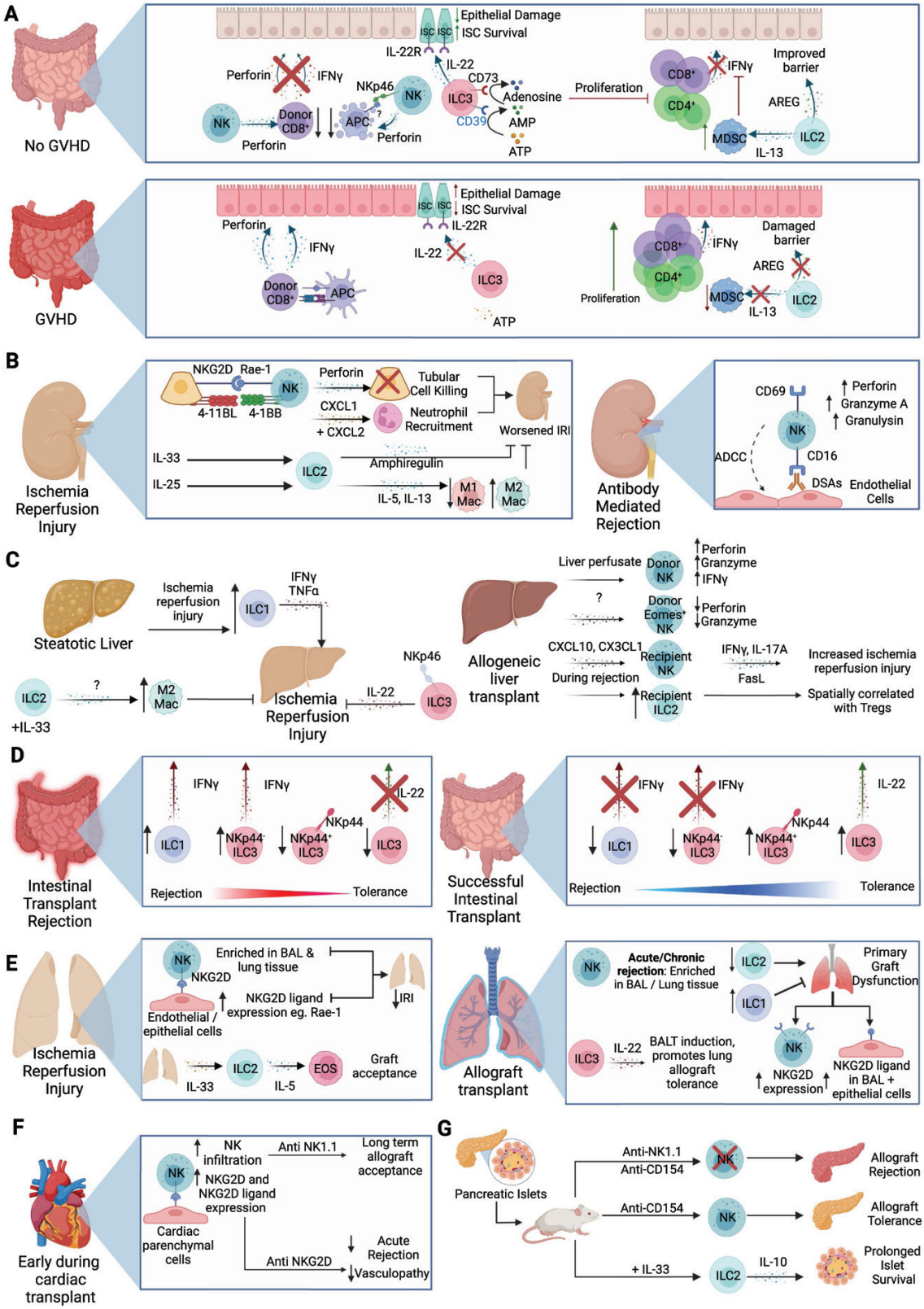

Figure 3. Overview of ILC functions in transplantation. (A) ILCs can help protect from development of GVHD in numerous ways. NK cells inhibit APC in the intestines, reducing activation of $CD8^+$ T cells. NK cells also target alloreactive $CD8^+$ T cells directly, preventing damage to intestinal epithelial cells. ILC3s produce IL-22 in the intestines which protects $IL\text{-}22R^+$ intestinal stem cells from destruction. Additionally intestinal ILC3s express ecto-enzymes CD39 and CD73, which degrade inflammatory extracellular ATP into adenosine to suppress immune responses. *In vitro* expanded mouse ILC2s have dual roles; both improving intestinal barrier function through production of amphiregulin (AREG) and expanding local MDSCs via IL-13, which in turn limit T-cell accumulation and suppress IFN-γ responses. (B) During renal ischemia reperfusion injury (IRI), interactions between tubular epithelial cells (TECS) and NK cells exacerbate IRI. This effect is mediated by perforin and is induced via NKG2D/Rae-1 interactions. The interaction of 4-1BB on NK cells and 4-1BBL on TECs results in the production of CXCL1 and CXCL2 leading to neutrophil recruitment that worsens IRI. In contrast, transferring ILC2s or

supporting ILC2s may act on both immune and non-immune cells to protect following HSCT(Fig. 3A). These intriguing findings should be further investigated in human studies, as well as contrasted with other ILCs to delineate unique contributions ILC subsets to protection following HSCT.

ILCs in kidney transplant

End stage kidney disease affects over 840 million individuals globally [83, 84], with kidney transplantation being the optimal treatment. IRI and ABMR remain major challenges in kidney transplantation efficacy. While ILCs have essential functions in CMV infection and tissue homeostasis [85–90], several studies have reported circulating recipient NK cells infiltrate the kidney and exacerbate renal IRI [91–94]. For example, depletion of NK cells using anti-asialo GM1 or anti-NK1.1 antibodies ameliorated IRI in mouse models [91, 92](Fig. 3B) and expression of 4-1BB on murine NK cells and 4-1BBL on tubular epithelial cells (TECs) was reported to promote TEC CXCL1 and CXCL2 production, resulting in neutrophil recruitment that exacerbated IRI [93]. *In vitro*, NKG2D-Rae-1 interactions direct NK cells to lyse renal TECs in a perforin-dependent manner. As TECs upregulated Rae-1 *in vivo* following IRI, this provides a possible mechanism by which NK cells contribute to IRI [91] (Fig.3B).

NK cells have also been linked to ABMR [95–97]. In mouse studies, donor-specific antibodies (DSAs) triggered activated NK cells to mediate acute rejection [98]. This was attributed to alloreactive NK cell activation from lack of self-recognition, resulting in NK cells interacting with DSAs to target endothelial cells via ADCC [99]. NK cells isolated from ABMR patients upregulated CD69 expression, and had elevated expression of perforin, granzyme A, and granulysin [100] (Fig. 3B). Of note, mismatched KIRs and KIR ligands are associated with a 25% reduction in 10-year graft survival [101] and NK cells may be resistant to conventional immunosuppression such as cyclosporin A, methylprednisolone, hydrocortisone, and azathioprine [102], highlighting that targeting NK cells in kidney transplant may be important to improve clinical outcomes.

In contrast to NK cells, recent studies indicate potential protective roles for ILC2s in kidney transplantation. Utilizing a mouse renal IRI model, Cao *et al.* reported that transferring ILC2s prior to or following IRI minimized tubular injury and serum creatinine, an effect dependent on amphiregulin and similar to that observed with IL-33 administration [103] (Fig. 3B). Separate studies showed that IL-25 alone or in combination with IL-2 and IL-33 co-administration improved IRI outcomes via ILC2-induced M2 macrophage activity(Fig. 3B), which was abrogated with depletion of ILC2s via anti-CD90 antibodies [104, 105]. In contrast, Cameron *et al*. reported no differences in IRI severity when multiple approaches to deplete or limit ILC2s were used [106]. The authors suggested this may be due to other immune populations being able to compensate for the loss of ILC2s. Although differences in the mouse models may underlie these conflicting findings, a key question is whether functions of ILC2s and other helper ILCs in allogeneic contexts remain unchanged. Studies are therefore needed to evaluate whether helper ILC populations contribute to or protect from allograft rejection or allogeneic IRI.

ILCs in liver transplant

The liver possesses a complex array of liver-resident immune cells that exhibit unique functions. This includes populations of cytotoxic and non-cytotoxic ILCs that are involved in promoting homeostasis and immune tolerance [107–109]. Liver-resident NK cells comprise 30–50% of hepatic lymphocytes [110, 111] and in humans, include conventional NK cells and $CD56^{bright}$ NK cells that express CCR5, CXCR6, CD69, and *EOMES*. Recent studies have further identified CD7, *KLRD1*(CD94), and *NCR1*(NKp46) as additional defining features of liver-resident NK cells [112, 113], which are localized to hepatic sinusoids [114, 115].

Liver-resident NK cells are well-described for their ability to promote immune tolerance, and can directly inhibit hepatic T cells [116]. In a murine lymphocytic choriomeningitis virus model, transfer of liver-resident NK cells decreased hepatic T-cell activity and impaired viral clearance, in contrast to conventional NK cells that promoted T-cell activity and viral

administrating IL-33 to promote ILC2 development attenuated IRI, an effect dependent on ILC2-derived amphiregulin. When administered IL-25, mouse ILC2s also promoted a Th2 response that induced alternatively activated macrophages which were tissue-protective in IRI. During antibody mediated rejection, NK cells can interact with donor specific antibodies to damage endothelial cells through antibody dependent cell-mediated cytotoxicity (ADCC), and express increased levels of perforin, granzyme A, and granulysin. (C) Using a mouse model of steatotic livers, ILC1s increase with IRI and have increased IFN-γ and TNF-α production that promote tissue injury. In a standard IRI model, administration of IL-33 increases ILC2s, leading to an enrichment of M2 macrophages that decrease damage associated with IRI. $NKp46^{+}$ ILC3s can reduce hepatic IRI via IL-22. In liver transplant, liver perfusate NK cells exhibit higher expression of perforin, granzymes and IFNγ that may enable them to protect the graft by inhibiting allogeneic immune responses. Conversely, long lasting resident NK cells with high EOMES expression and lower cytotoxic potential are also observed, which may promote long term allograft acceptance as the presence of NK cells following liver transplant is associated with immune tolerance following withdrawal of immunosuppressants. However mouse models of liver transplant suggest increased infiltration of recipient NK cells induced by CXCL10 and CX3CL1 promotes liver IRI through elevated IFN-γ, IL-17A and FasL. ILC2s are increased during rejection and found in proximity to CD4+ regulatory T cells (Tregs), suggesting they are either recruiting or supporting Tregs. (D) In acute cellular rejection, accumulation of IFN-γ producing ILC1s and $NKp44^{-}$ ILC3s were observed, with a reciprocal decrease in IL-22 producing and $NKp44^{+}$ ILC3s. In contrast, increased $IL\text{-}22^{+}$ $NKp44^{+}$ ILC3s is associated with graft tolerance. (E) NK cells are enriched within the broncho-alveolar lavage (BAL) and lung tissue during IRI. NKG2D expression by NK cells interacts with Rae-1 on endothelial and epithelial cells during IRI, and blocking the NKG2D receptor or depleting NK cells reduces IRI-induced pathology. IL-33 expression following IRI increases ILC2s within the graft. These ILC2s recruit eosinophils through IL-5 production and can promote allograft tolerance in mice. NK cells increases in the BAL or lung tissue during acute or chronic rejection respectively. The production of IL-22 by ILC3s led to the formation of bronchus associated lymphoid tissue (BALT) and promoted allograft tolerance. In primary graft dysfunction, NKG2D and NKG2D ligand Rae-1 expression is increased on NK cells and epithelial cells, respectively. The development of primary graft dysfunction is correlated with decreased ILC2s and increased ILC1 prior to transplant. (F) Early on in cardiac transplant, NK cells infiltrate the allograft, with increased NKG2D expression by NK cells and NKG2DL by cardiac parenchymal cells. Depletion of NK cells or blocking NKG2D in CD28-deficient mice led to increased cardiac graft survival and attenuated acute allograft rejection and allograft vasculopathy. (G) In a mouse model of islet transplant, treatment with IL-33 expands IL-10 producing ILC2s that can limit allograft rejection and adoptive transfer of IL-10-producing ILC2s blocked islet rejection. NK cells may also have protective functions, as anti-NK1.1 treatment resulted in rejection of transplanted islets in mice receiving anti-CD154 treatment. Created with Biorender.com.

clearance [116]. This inhibition of T-cell function was dependent on PD-1 and PD-L1 on T cells and liver-resident NK cells, respectively(Fig. 2) [116]. Liver NK cells are also characterized by decreased inflammatory potential in both mice and humans, possessing reduced ability to produce IFN-γ and respond to IL-12 or IL-18 stimulation, while also being a source of IL-10 [117, 118]. Interestingly *in vitro* studies by Jinushi et al. demonstrated that circulating NK cells can be induced to produce immunosuppressive cytokines IL-10 and TGF-β when co-cultured with hepatocytes via NKG2A receptor engagement with HLA-E on hepatocytes [119] (Fig. 2).

Depending on the context, liver resident NK cells were reported to promote or inhibit liver regeneration. In studies using immunodeficient mice receiving partial hepatectomy, optimal liver regeneration required NK cells, and blocking NKG2D reduced hepatocyte proliferation [120]. In contrast to these findings, depleting NK cells in C57BL/6J mice using anti-asialo- GM1-antibody enhanced liver regeneration [121]. These differing findings could relate to the degree of NK cell activation, as following liver injury, NK cells in *Tigit*$^{-/-}$ mice had increased activation and IFN-γ production which impaired liver regeneration [122]. As new data emerge on the distinct subsets of liver NK cells [113, 123, 124], it will be important to delineate the role of individual NK cell populations in liver regeneration, as these differing reports may be due to distinct NK cell subpopulations being activated depending on the model.

Liver resident NK cell functions have also been explored in the context of transplantation. Analysis of human liver perfusate NK cells before transplant reported that CD56^{bright} NK cells have high perforin and granzyme expression compared to circulating NK cells, express CD69 and IFN-γ, and exhibit enhanced cytotoxic potential [125]. *In vitro* studies where liver-resident CD56^{bright} NK cells could kill allogeneic CD8^{+} T cells [126], supports liver NK cells may protect the graft during the acute phase post-transplant by inhibiting allogeneic adaptive immune responses. Notably, a lower percentage of NK cells in the liver perfusate prior to transplant is observed in recipients with acute cellular rejection(ACR) compared to those that did not [127].

While increased proportions of circulating NK cells following liver transplant are correlated with improved operational tolerance following immunosuppression withdrawal [128], these effects may also extend to liver-resident NK cells. For example, donor NK cells can persist within the liver allograft for at least 13 years following transplant and exhibit decreased levels of perforin and granzymes [129] and hypofunctionality [130] (Fig. 3C). Furthermore, introducing donor-derived liver NK cells into rats prolonged allograft survival and reduced histological damage, collectively supporting donor-derived NK cells may possess a role in limiting host versus graft response and promoting long-term allograft acceptance [131]. The same is not necessarily true for recipient-derived infiltrating NK cells. Using a model of rat orthotopic liver transplant, Obara *et al.* demonstrated early following transplant the liver allograft upregulates CXCL10 and CX3CL1 to recruit recipient circulating recipient NK cells with increased IFN-γ compared to donor NK cells [132] (Fig. 3C). Depletion of NK cells via an anti-asialo GM1 antibody prolonged allograft survival, indicating that infiltrating NK cells acquire a pro-inflammatory signature that contributes to rejection [132]. Infiltrating recipient NK cells were separately shown to promote liver IRI through IFN-γ, IL-17A, and FasL, which was reversed when depleting NK cells using anti-NK1.1 or anti-asialo GM1 antibodies [132–134] (Fig. 3C). Taken together, these murine studies support recipient NK cells are detrimental, whereas donor-derived liver NK cells are protective, highlighting a key difference between NK cells from the donor or recipient.

ILC1s represent the most abundant helper ILC population in the human liver [109], and localize to the perivascular spaces near DCs where they produce IFN-γ downstream of DC-derived IL-12 in viral infection [135, 136]. Similar to NK cells, ILC1s can also control T-cell activity. For example, in a murine hepatitis B virus model, ILC1s limited HBV-specific CD8^{+} T cell proliferation by controlling IL-2 availability [137] (Figure 2). Beyond regulating T-cell responses, adoptive transfer of ILC1s into immunodeficient mice protected from CCL4-mediated liver injury in a mechanism whereby ILC1-derived IFN-γ increased Bcl-xL expression by hepatocytes [138]. In contrast to these findings, ILC1s worsened IRI-induced tissue damage in a high-fat diet model of steatotic liver disease, where induced IRI resulted in elevated ILC1 numbers that had increased IFN-γ and TNF-α production [139] (Fig. 3C), and IRI studies using immunodeficient and ILC1 knockout mice resulted in decreased IRI-induced pathology [139]. Further studies are needed to clarify ILC1s functions in IRI, particularly in humans, as well as examine if these functions are maintained in allogeneic contexts.

While allogeneic studies on ILC1s are lacking, hepatic ILC2 was reported to significantly increase with rejection in a model of orthotopic liver transplant. ILC2s present within the allograft were of recipient origin and were spatially found in close proximity with liver Tregs, suggesting ILC2s may be attempting to inhibit allograft rejection or respond to damage [140]. In a murine IRI model, IL-33 treatment activated ILC2s that in turn increased M2 macrophage liver accumulation, leading to decreased hepatic damage [141] (Fig. 3C), suggesting possible protective roles ILC2s in liver transplant. However, ILC2s have also been linked to liver fibrosis. Chronic hepatocyte stress upregulated IL-33 that activated mouse ILC2s which in turn produced IL-13 that drove fibrosis [142], indicating that ILC2s protective effects may be context specific.

Current studies support the protective functions of ILC3s in the liver. ILC3s signature cytokine, IL-22, was shown across multiple studies to promote liver regeneration [109, 143, 144]. Using a mouse model of hepatic IRI, mice deficient in NKp46^{+} IL-22^{+} cells that resemble ILC3s experienced severe IRI, a phenotype that was reversed with adoptive transfer of these NKp46^{+} cells [144] (Fig. 3). Furthermore, in a murine hepatitis model, RORγt-deficient mice that lack IL-22^{+} ILC3s experienced more severe hepatitis [145]. Although the role of ILC3s in allogeneic contexts has yet to be determined, these studies collectively support ILC3s functions in promoting liver regeneration which may have important implications for transplantation.

ILCs in intestinal transplant

Intestinal failure is a life-threatening condition primarily caused by intestinal resections performed to treat inflammatory bowel disease, cancer, or intestinal dysmotility [146]. Intestinal transplants have been increasingly used

due to severe catheter-related infections and risk of patients developing metabolic complications [146]. While the success of intestinal transplants has improved, only 50% of grafts remain functional at 5-years [147], due to a wide variety of complications including sepsis, ACR, ABMR, posttransplant lymphoproliferative disorder, IRI, and GVHD [148].

Many complications stem from lymphoid cells present within transplanted tissue, as well as the complex immune network in the gut-associated lymphoid tissue [149]. This includes DCs which stimulate anti-graft lymphocytes, B cells that produce DSAs causing ABMR, and cytotoxic T and NK cells driving ACR. Shortly after transplant, a substantial increase in recipient ILCs in the epithelium and lamina propria is observed in recipients compared to healthy controls [150, 151], which is maintained up to a decade after transplant, gradually skewing towards recipient-derived ILCs [151, 152]. Allograft-resident ILCs are primarily NK cells, ILC1s, and ILC3s, with elevated IFN-γ^+ and IL-22$^+$ CD3$^-$ intraepithelial lymphocytes, and an increased cytotoxic profile compared to healthy individuals [150]. Despite the cytotoxic profile, none of the grafts in this study failed and patients did not experience infections, suggesting this profile is consistent with successful transplants [150]. Indeed, other studies noted elevated helper ILCs in patients with healthy grafts and those with rejection [151, 152]. Interestingly, Gomez-Massa *et al.* biopsied a single patient weekly to evaluate ILC replacement kinetics and observed that once the patient progressed to ACR, there was an expansion of ILC1s and a decrease of ILC3s [151]. This could indicate that while an elevation of ILC1s and ILC3s compared to native intestine is beneficial for graft success, a shift in ILC1-ILC3 balance or changes in ILC subpopulations may lead to rejection (Fig. 3D). Separately, patients who developed ACR were reported to have similar proportions of ILC1s, ILC2s, and total ILC3s compared to patients without rejection and healthy controls, however, a decrease in specifically NCR$^+$ILC3s and a reciprocal increase in NCR$^-$ILC3s was observed [153]. Further supporting ILC3s' importance for intestinal transplant tolerance, when Kang *et al.* compared ILCs between stable and rejecting allografts, a stark decrease in NCR$^+$ILC3s and an increase in ILC1s occurred in rejecting allografts [154]. Collectively, these data show that a healthy ILC compartment is important for prevention of graft rejection, with NCR$^+$ILC3s being associated with protection.

ILCs in lung transplant

Within the lungs, all ILC subsets are present and have important functions in host defense; NK cells make up 10% of total lymphocytes and are predominantly CD56^{dim}CD16$^+$. Lung NK cells display hyporesponsiveness to stimulation and express more KIRs than circulating NK cells [155]. Other ILCs are also present, with ILC2s and ILC3s comprising the majority of non-cytotoxic ILCs in the lung [156].

During lung transplants, NK cells have been linked to lung allograft failure. NK cell numbers were significantly elevated in bronchoalveolar lavage (BAL) or lung biopsy samples collected from recipients with acute or chronic lung allograft rejection, respectively [157, 158]. In a separate study, an increase of NK cells in areas of lung IRI was noted, which could also be detected in the BAL [159] (Fig. 3E). These human findings were supported by mouse studies, where NK cell-deficient mice had reduced IRI-induced pathology and adoptive transfer of NK cells worsened IRI [159]. NKG2D receptor ligands are present on lung endothelial and epithelial cells following IRI, and blocking the NKG2D receptor similarly reduced IRI, supporting a role for NKG2D in controlling NK cell responses to the lung graft [159] (Fig. 3E). In a murine tracheal transplant model, depletion of NK cells or inhibition of NKG2D attenuated bronchiolitis obliterans in recipients [160], a finding supported by studies of patients with primary graft dysfunction, where NKG2D ligands were enriched in airway epithelial cells and NKG2D was upregulated on NK cells [161, 162]. However, NK cells have also been shown to promote lung transplant tolerance. In a murine model of lung transplant, recipient NK cells expanded with IL-15/IL-15-Ra complex killed allogeneic APCs and protected from rejection, [163] and in humans, HLA-mismatched NK cells correlated with improved outcomes of lung transplantation [164]. These contrasting reports may reflect differences in donor and recipient NK cells, specific NK cell populations, as well as unique donor–recipient interactions. As NK cells are a highly heterogeneous population, additional studies mapping specific subsets of NK cells and their source are needed.

Although helper ILCs functions in lung infection and inflammation have been described (Fig. 2), there are comparatively fewer studies assessing ILCs role in lung allograft tolerance [25, 165, 166]. Monticelli *et al.* reported the development of primary graft dysfunction is associated with a marked reduction in ILC2s following reperfusion, and patients that did not develop primary graft dysfunction had higher ILC1 frequencies prior to allograft reperfusion [167] (Fig. 3E). In a murine lung transplant model, ILC2s facilitated lung allograft acceptance through eosinophil recruitment via IL-5 production [168] (Fig. 3E). This is intriguing, as ILC2-mediated eosinophilia has been associated with lung inflammation in asthma and other lung pathologies [169–173], yet eosinophilia in models of murine lung transplant has been shown to promote immune tolerance, suggesting that the effects of ILC2 mediated eosinophilia may be context dependent [174]. While not studied in allogeneic context, Seehus *et al.* report IL-10-producing ILC2s can serve as "tissue sentinels" able to rapidly produce IL-10 to limit immune responses [175]. Whether IL-10-producing ILC2s are protective in lung transplantation is not known, and further investigation is needed to determine if specific ILC2 cytokines support transplant tolerance, or if distinct ILC2 populations are protective.

In the human lung, ~60 % of helper ILCs are ILC3s, with NCR$^-$ ILC3s being the predominant ILC population [156]. While studies of ILC3s in human lung transplantation are lacking, murine transplant models support that ILC3s within lung allografts are crucial producers of IL-22 that promotes allograft tolerance [176] (Fig. 3E). Interestingly, lung ILC3s may also directly regulate T-cell responses within the lung. Mouse ILC3s that express MHC class II inhibited CD4$^+$ T-cell responses to allergen, thereby limiting airway inflammation [166] (Fig. 2). Whether ILC3s could regulate allogeneic T-cell responses within the lung remains to be examined, but the possibility of lung ILC3s exhibiting antigen-presenting capabilities warrants investigation into whether this may occur in the transplant setting.

ILCs in cardiac transplant

Studies of ILCs in the human heart are rare, due in part to the complexity and scarcity of cardiac transplant samples. However, cardiac ILC functions were explored at the steady

state in mouse models [177–179] (Fig. 2), where NK cells represent 3% of immune cells, ILC2s 1.7%, and ILC1s represent 0.2%, with no ILC3s being detected [180]. Parabiosis and adoptive transfer experiments suggest the proportion of heart ILCs remains stable during homeostatic and inflammatory conditions, implying that circulating ILC progenitors do not infiltrate and alter ILC proportions [180, 181]. Studies in humans corroborate these findings and indicate that a large proportion of non-cytotoxic ILCs are committed cardiac ILC2 precursors. Following ischemic cardiomyopathy or myocarditis, this ILC2 precursor population decreases, and levels of differentiated ILC2s increase, suggesting a mechanism whereby ILC2 precursors are locally activated and differentiate in response to tissue injury [181].

NK cells are the most well-characterized ILC population within cardiac transplantation and are reported to contribute to allograft rejection. Early following transplant, murine NK cells comprise the predominant population of infiltrating lymphocytes, and NKG2D ligands are upregulated in cardiac tissue [182, 183] (Fig. 3F). Early studies involving CD28-deficient mice show that while these mice reject cardiac allografts in a CD8-T-cell mediated mechanism, depletion of NK cells using an anti-NK1.1 antibody prolongs graft survival and established long-term allograft acceptance [184] (Fig. 3F). Blocking the NKG2D receptor was also able to abrogate acute allograft rejection [185], an observation that was replicated in the context of antibody-dependent rejection [186] (Fig. 3F). In addition, separate studies demonstrated NK cells contribute to cardiac allograft vasculopathy through CD16-dependent activation and IFN-γ responses [187, 188]. While human studies are needed, there is consensus from mouse studies to date that NK cells are harmful in cardiac transplants.

ILCs in pancreas and islet transplant

Beta-islet cell (β-cell) replacement therapy is used to treat patients with type 1 diabetes who cannot be stably treated with external insulin [189]. Replacement therapy involves either a whole pancreas transplant requiring major surgery, or the less invasive islet transplantation which can be done laparoscopically [190]. While these are life-changing therapies, both approaches do not resolve underlying immunopathology and recipients require life-long immunosuppression to prevent graft loss [191].

Beilke *et al.* reported a mouse NK1.1$^+$ILC population-induced islet allograft tolerance following anti-CD154 antibody treatment [192]. Perforin$^{-/-}$ mice were unable to induce tolerance, suggesting this NK1.1$^+$ILC was an NK cell, and supporting NK cell-mediated tolerance involved a cytotoxic mechanism (Fig. 3G). Similarly, induction of islet tolerance using anti-CD45RB and anti-Tim-1 antibodies required both regulatory B cells and NK1.1$^+$ cells for allograft tolerance, and tolerance could be restored with wild-type NK cell infusion [193].

In models of pancreatic stress, ILC2s may have protective capabilities or improve islet function. In mice treated with streptozotocin to induce β-cell destruction, increased *IL33* expression was observed in pancreatic mesenchymal cells which activated ILC2s [194]. ILC2s in turn produced IL-13 and GM-CSF, inducing myeloid cells to secrete retinoic acid that increased β-cell insulin secretion [194]. In a murine islet transplant model, IL-33 injection protected from allograft rejection via expansion of IL-10 secreting ILC2s, and adoptive transfer of mouse ILC2s inhibited allograft rejection [195] (Fig. 3G). While promising, additional studies contrasting ILC2s with other ILCs are needed, as are human studies to understand if adoptive transfer of ILCs could limit rejection of transplanted islets.

Harnessing or targeting ILCs to promote transplant tolerance

ILC family members have important roles in tissue homeostasis and immune tolerance. To date, therapeutics that specifically target or harness ILCs have not been used clinically, however, a growing body of evidence supports targeting or harnessing ILCs populations may have applications for transplantation. This includes the possibility of harnessing ILC2 or ILC3s dual reparative and tolerance-promoting functions. Several potential methods of manipulating ILCs have been suggested, including using cytokine and cytokine receptor agonists, targeting receptors expressed by specific subsets using monoclonal antibodies, and even using ILCs in adoptive cell therapies.

Studies of cytokine-based approaches include those where IL-33 injection results in a short-term expansion of ILC2s that protect from islet graft rejection and acute colitis [195, 196]. Expansion of IL-10-producing ILC2s was enhanced with IL-33 co-administration with IL-2/anti-IL-2 receptor antibody complex and prevented rejection in an islet transplant model or decreased renal IRI [43, 195]. Similarly, IL-1β, IL-23, and retinoic acid promoted ILC3 differentiation from ILC1s, which could potentially correct aberrant ILC1 to ILC3 ratios [151, 197]. Similar approaches have been used to expand or activate NK cells, CD8$^+$ T cells, and Th2 cells in a variety of contexts [163, 198], although identifying cytokines that selectively expand protective ILC populations without acting on other immune populations remains challenging.

Adoptive cell transfer of expanded ILCs with immunoregulatory potential has been explored in multiple transplant contexts. Huang *et al.* transferred *in vitro* expanded IL-10-producing murine ILC2s into mice shortly before and after islet transplant, which could migrate to the allograft and limit rejection [195]. Similar results were seen in murine GVHD, where infused ILC2s localized in the intestines and indirectly suppressed GVHD through IL-13-mediated MDSC expansion [82]. Additionally, adoptive transfer of mouse ILC2s limited renal IRI in an amphiregulin-dependent manner, supporting ILC2's dual reparative role could be harnessed for transplantation [103]. Whether ILC3s might have similar beneficial effects in adoptive cell therapies for transplant has not been explored to date, but has been examined in autologous contexts. For example, in a model of experimental type 2 diabetes during *Mycobacterium tuberculosis* infection, adoptive transfer of IL-22$^+$ILC3s or LTi cells improved mouse survival [199], and adoptive transfer of NKp46$^+$IL-22 producing ILCs minimized liver IRI [144].

Challenges and limitations of ILC research and clinical applications

Limiting translation of adoptive ILC-based therapies to humans is the relatively small numbers of ILCs in peripheral blood, which is typically the source of immune cells for cell therapy. Helper ILCs generally comprise 0.1% of circulating

lymphocytes and 0.5% of lymphocytes in cord blood [8]. While several groups have developed protocols for the generation of ILCs from $CD34^+$ cord blood or ILC precursor populations, these expansions result in a mixed ILC population [7, 200]. Separate studies have expanded human ILC3s (referred to as NK22 cells in the study) and ILC2s *in vitro*. While achieving robust fold expansions, these methods have not been able to obtain sufficient numbers for clinical translation [201, 202].

While NK cells have been widely associated with protection from GVHD following HSCT, and protective in mouse models of islet transplant, they are associated with IRI-induced pathology and rejection in kidney, liver, and cardiac transplant. These varying results across transplant types might be explained by organ-adapted functions of ILCs, and suggest protective or harmful ILC populations could differ between tissues. Human studies examining differences in ILC functions within organ allografts of those with and without rejection are needed to define local ILC responses, not just tracking the presence or absence of ILC family members. Further complicating this, is the diversity of circulating and resident ILC populations between individuals. Even within circulating $CD56^{dim}$ and $CD56^{bright}$ NK cells, there are large variations in phenotypes [203], with overlapping markers of other ILC family members [20], thereby complicating interpretations of early correlative studies of clinical outcomes with NK cell phenotypes. This in turn creates challenges for development of therapeutics targeting NK cells, as both protective and harmful subpopulations of NK cells may be present. New approaches such as single-cell RNA sequencing (scRNAseq)-based technologies are being applied across organs to assess responses that underly rejection and those which occur in healthy individuals. This will allow for better delineation of phenotypic and functional heterogeneity of NK cells and all ILCs in transplantation, which will be important to resolve NK cell populations that drive harmful responses or improve graft outcomes.

Importantly, current immunosuppression has been mostly studied in the context of inhibiting B- and T-cell responses, with some evidence suggesting NK cells and helper ILCs may be resistant to current immunosuppression [102]. Alemtuzumab, an anti-CD52 humanized monoclonal antibody, and polyclonal rabbit anti-thymocyte globulin have been used to treat patients following kidney and pancreas transplantation, resulting in a marked loss of circulating NK cells that exhibited decreased cytotoxicity and increased apoptosis [204]. However, both therapies are unable to target $CD52^-$ NK cells found within liver and also deplete T and B cells [205]. A more specific approach that targeted NK cells and $CD8^+$ T cells using anti-NKG2D and anti-CTLA improved allograft survival in a mouse model of islet transplant [206], and similar improvements were seen by blocking NKG2D in *in vitro* models of airway epithelial cytotoxicity [161]. This emphasizes the possibility of using targeting antibodies to prevent NK cell-mediated IRI and organ rejection. As new data emerges on ILC metabolism, microbiome-derived metabolites effects on ILC functions, chemokines that control ILC trafficking, impact of MHC expression by helper ILCs in allogeneic contexts, and molecules that activate or inhibit ILCs, novel approaches may emerge that more specifically promote ILCs reparative functions, blocking harmful NK cell responses or promoting tolerogenic ILC expansion or activation.

Tissue tolerance is mediated by complex interplay between the various immune cells including DCs [207, 208], mast cells [207], macrophages [209], eosinophils [174, 210], B cells, [211] and ILCs. For example, IFN-γ can induce $iNOS^+$ eosinophils that are protective in lung transplantation and infiltrate early after transplant [210]. ILC2s are similarly protective in lung transplantation, yet they are constrained by IFN-γ [212]. Intriguingly, ILC subsets have been shown to interface with many of these cells and promote regulatory functions [5, 213]. Moving forward, it will be important to disentangle the network of cells and pathways in each organ that leads to protection from adverse outcomes following organ transplantation and explore how ILC family members contribute to these circuits across different tissues. Of particular interest is the role of ILC-Treg crosstalk in promoting tolerance. Currently, the interplay between these immune populations is not well understood in the context of transplantation, but evidence from autologous settings indicates ILCs could work collaboratively with Tregs to promote tolerance. For example, in mice, IL-9 from ILC2s was crucial for activation of Tregs and resolution of inflammation in an arthritis model [214]. In resting or helminth-infected adipose tissue, IL-33 stimulated ILC2s induced Treg activation and accumulation through ICOSL-ICOS interactions [215]. Similarly, ILC3s in the intestine are an important source of IL-2, which supports intestinal Treg maintenance [216] and GM-CSF, which helps maintain Treg homeostasis through DCs and macrophages [217]. It will therefore be important to examine ILC-Treg crosstalk and consequences for tissue tolerance.

A major limitation of our current understanding of the role of ILCs in organ transplantation and HSCT is that most studies have been correlational. While scRNAseq studies investigating human transplantation are shedding new light into the cells and pathways that drive tolerance, these only capture a single point in time, missing important temporal observations of early immune responses that drive organ rejection or promote tolerance. Rodent models of organ transplantation have been essential in bridging the gap between correlational patient data and mechanisms underlying organ transplant and tolerance. Unfortunately, these models do not accurately reflect the diverse human population, and thus have limitations for translation of insights gained from these models [218]. A further complication for the field of ILCs is the differences between mouse and human ILC subsets including markers to identify them, specific functions, and responses to environmental triggers [219]. To gain a better understanding of the functional role of human ILCs in transplantation, newer humanized mouse models, as well as *ex vivo* approaches such as precision cut-tissue slice models, organoids, organ-on-a-chip, and 3D cultures should be harnessed to better define human ILC interactions with allogeneic tissues and other immune populations that contribute to protective or pathogenic immune responses to organs. This, combined with powerful new single-cell and spatial technologies, will provide valuable insights into mechanisms by which human ILCs coordinate transplant immune responses, which may one day lead to novel therapeutic approaches for transplantation.

Supplementary Data

Supplementary data is available at *Clinical and Experimental Immunology* online.

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Figures were created with BioRender.com.

Ethical Approval

Not applicable.

Conflict of Interests

The authors declare that they have no competing financial interests. K.T.R and S.Q.C have filed a provisional patent for human ILC expansion methods (Provisional Patent Application#: 63/353,823).

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M.L.M and K.T.R. both contributed equally to the work. All authors wrote and edited the manuscript.

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Data availability

Not applicable.

Clinical Trial Registration

Not applicable.

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