Published in final edited form as:

Curr Opin Organ Transplant. 2019 February ; 24(1): 49–57. doi:10.1097/MOT.0000000000000594.

Why some organ allografts are tolerated better than others: new insights for an old question

Travis D. Hull^a, Gilles Benichou^b, and Joren C. Madsen^{a,b,c}

^aDepartment of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts USA

^bCenter for Transplantation Science, Harvard Medical School, Boston, Massachusetts USA

^cDivision of Cardiac Surgery, Department of Surgery, Massachusetts General Hospital, Harvard Medical School, Boston, Massachusetts USA

Abstract

Purpose of review—There is great variability in how different organ allografts respond to the same tolerance induction protocol. Well known examples of this phenomenon include the protolerogenic nature of kidney and liver allografts as opposed to the tolerance-resistance of heart and lung allografts. This suggests there are organ-specific factors which differentially drive the immune response following transplantation.

Recent findings—The specific cells or cell products that make one organ allograft more likely to be accepted off immunosuppression than another are largely unknown. However, new insights have been made in this area recently.

Summary—The current review will focus on the organ-intrinsic factors that contribute to the organ-specific differences observed in tolerance induction with a view to developing therapeutic strategies to better prevent organ rejection and promote tolerance induction of all organs.

Keywords

mechanisms; organ-specificity; tolerance

INTRODUCTION

Whereas kidney allograft tolerance has been achieved in nonhuman primates (NHPs) [1–3] and in humans [4–7], protocols that achieve tolerance of kidney allografts in NHPs fail to induce tolerance of heart allografts [8]. The reasons for this organ-specific difference are not clear. However, it is clear that all transplanted organs are *not* created equal. Not only does the strength of the immune response to a particular organ vary with the organ transplanted but the nature of response itself, rejection versus tolerance, varies from organ-to-organ. In

Correspondence to Joren C. Madsen, MD, DPhil, Department of Surgery, Massachusetts General Hospital, 55 Fruit Street, WHT-05-510C, Boston, MA 02114, USA. Tel: +1 617 726 6506; jcmadsen@mgh.harvard.edu.

Conflicts of interest

There are no conflicts of interest.

most experimental transplant models, kidney, and liver allografts evoke a weaker rejection response than heart and lung allografts. Moreover, kidney and liver allografts can actively participate in the induction and maintenance of tolerance and thus, can be considered ‘tolerance-prone’ organs. The same cannot be said for heart and lung allografts which are, for the most part, ‘tolerance-resistant.’ Finally, kidney and liver allografts also possess the unique ability to confer unresponsiveness upon cotransplanted, tolerance-resistant organs like hearts. Understanding the mechanisms underlying these organ-specific differences could contribute to the development of strategies that extend tolerance to recipients of tolerance-resistant organs. Here, we review organ-specific differences in tolerance induction, focusing on the dissimilarities between tolerogenic kidney and liver allografts and the more stringent heart and lung allografts.

ORGAN DIFFERENCES IN THE DEVELOPMENT OF OPERATIONAL TOLERANCE FOLLOWING WITHDRAWAL OF IMMUNOSUPPRESSION

Operational tolerance in solid organ transplantation, defined as spontaneous graft acceptance without histological evidence of rejection for at least 1 year after cessation of immunosuppression [9], has been observed in human kidney and liver transplant recipients [10] with clear benefits to quality of life [11]. Examination of the natural history of 27 kidney transplant patients rendered operationally tolerant after withdrawing immunosuppression revealed that 70% maintained stable graft function for an average of 9 years after transplantation [12]. In adult liver transplantation, 5–33% of patients who withdraw from immunosuppression exhibited operational tolerance [13–17], although the incidence was higher in the pediatric population [18]. In contrast, there exist only anecdotal cases of operational tolerance in a lung recipient or heart recipient [19].

Similar differences have been observed in the spontaneous acceptance of murine organ allografts transplanted into untreated recipients. Murine skin, hearts, intestines, lungs, and hepatocytes are largely rejected when transplanted across multiple major histocompatibility factor (MHC) barriers [20–24]. In contrast, kidneys and livers are commonly accepted across the same MHC barriers [21,25–30]. In a direct comparison of liver, kidney, and heart allograft survival after transplantation across the same full MHC disparities in untreated murine recipients, most of liver allografts (57–72%) were spontaneously accepted long-term, whereas hearts were all rejected in less than 10 days [21]. The pattern of kidney allograft rejection was mixed with 20–50% organs surviving long-term [21]. Among higher order animals, spontaneous tolerance has only been reported after liver [31] or kidney [32] transplantation in swine. These experimental results and others [33–36] support the fact that abdominal allografts have a much greater propensity for spontaneous acceptance compared with thoracic organs transplanted across the same MHC barrier.

ORGAN DIFFERENCES FOLLOWING THE ACTIVE INDUCTION OF ACQUIRED TOLERANCE

Organ-specific differences in the predisposition toward tolerance is even more pronounced when a tolerant state is actively induced using a variety of short-term immunosuppressive

protocols. For instance, MHC class I disparate hearts or fully mismatched hearts transplanted into miniature swine treated with 12 days of a calcineurin inhibitor (CNI), all rejected within 60 days [37,38]. In contrast, kidneys transplanted across the same genetic barriers and treated identically all became tolerant and maintained excellent renal function long-term [39,40]. The survival of lungs was in between that of hearts and kidneys with graft survival ranging from 67 to more than 605 days but with most developing obliterative bronchiolitis [41]. A similar dichotomy was observed in cynomolgus monkeys treated with a mixed chimerism conditioning regimen, wherein kidney allografts survived long-term while hearts or lungs allografts were rejected early despite the identical treatment and similar MHC disparities [3,8]. Thus, the ability to induce tolerance of an organ varies dramatically with the organ transplanted. The clinical implications of these findings are that successful tolerance protocols will not be directly transferable from one organ system to another and that the preclinical testing of tolerance protocols for human transplantation will have to proceed in an organ-specific manner [42].

TOLERANCE OF A RESISTANT ORGAN INDUCED BY COTRANSPLANTATION WITH A TOLERANCE-PRONE ORGAN

Even more striking than the apparent hierarchy in organ tolerogenicity, is the observation that tolerance-prone organs can confer unresponsiveness upon tolerance-resistant organs procured from the same donor. Using MHC inbred miniature swine, we have shown that instead of rejecting their hearts, recipients cotransplanted with hearts and kidneys from the same class I disparate [43] or fully MHC mismatched [38] donor developed stable tolerance after 12 days of a high-dose CNI. In addition to long-term, rejection-free survival of both kidney and heart allografts, there was no alloantibody formation or evidence of chronic rejection. Similar results have recently been observed in NHPs transplanted with heart alone or heart and kidney allografts undergoing mixed chimerism conditioning (M. Tonsho, article in preparation).

This phenomenon, now termed kidney-induced cardiac allograft tolerance (KICAT), is dependent upon several variables including MHC matching of the heart and kidney [44], presence of the host thymus [45], and the presence of a yet-to-be-determined radiosensitive cell population within the donor kidney [46]. Of note, cotransplanting a donor lung instead of a kidney with the heart did not prolong the survival of either graft [47] and transplanting two donor-matched hearts did not induce tolerance, indicating the KICAT was not a function of donor antigen load [48]. It is also noteworthy that donor nephrectomy 8 days after cotransplantation resulted in cardiac allograft vasculopathy (CAV) and rejection, reflecting the importance of the renal allograft during the induction phase of tolerance [49]. Donor nephrectomy 100 days after transplantation resulted in CAV but not rejection, suggesting that persistence of the donor kidney is necessary for durable tolerance without chronic rejection [49].

ROLE OF REGULATORY T CELLS

When the phenotypes of graft infiltrating lymphocytes retrieved from isolated porcine kidneys allografts were examined, the number of cells expressing the phenotypic markers of

T regulatory cells (Tregs) were substantially higher in acceptor than in rejector transplants at all time points [50]. Also, we have shown that CD25⁺ T cells in peripheral blood leukocytes from heart/kidney recipients but not isolated heart recipients could fully suppress the antidonor response of naïve-matched T cells in coculture cell-mediated lympholysis assays [51]. Based on these results and others [50,52,53], we hypothesize that cells or cell products intrinsic to kidney, but not heart, allografts promote the activation/expansion of host Tregs.

Together, these results suggest that cardiac allografts lack one or several soluble or cellular factor(s) present in the cotransplanted kidney which is able to enhance or augment host Tregs and thereby induce a robust state of tolerance. Once identified, this cell or factor(s), could be utilized to induce tolerance of all resistant organs. For this reason, the remainder of this review will focus on the factors intrinsic to toleranceprone organ allografts that may be responsible for promoting host regulatory mechanisms.

INTRINSIC MECHANISMS OF ORGAN-SPECIFIC DIFFERENCES IN TRANSPLANT TOLERANCE

The tolerance potential of a particular organ (it's tolerogenicity) is the product of intrinsic and, in the case of barrier organs like lung and intestine, extrinsic factors such as environmental antigens (reviewed in [54]). Intrinsic factors include organ homeostatic functions, cell-surface antigens, donor-derived, tissue-resident immune cells and their cell products, and soluble factors produced by parenchymal cells secondary to their normal physiological function.

Organ homeostatic functions

The propensity for a given organ to elicit a proinflammatory versus anti-inflammatory response after sustaining an insult or encountering allo-antigen likely contributes to its threshold for tolerance induction. This threshold is largely dependent upon the nature of the network of resident immunological cells including macrophages, dendritic cells, and selective subsets of adaptive immune cells found within the tissue parenchyma. For example, when the epithelium of the lung, a barrier organ, is presented with a respiratory pathogen, host survival depends upon generation of a robust inflammatory response. The generation of damage-associated molecular patterns secondary to respiratory infections in lung transplant recipients initiates an innate immune response through Toll-like receptors, resulting in the generation of proinflammatory cytokines and chemotactic responses, setting off a cascade of events that ultimately favor graft rejection [55–57]. Conversely, in tolerance-prone organs such as the liver and kidney, whose physiological functions include detoxifying and filtering the blood, resident immunological cells dampen the response to alloantigens and autoantigens to prevent tissue damage and autoimmunity [58]. Crosstalk between epithelial cells and the resident immunocytes appears to be a strong anti-inflammatory mechanism in the kidney. For instance, renal tubular epithelial cells (RTECs) exposed to proinflammatory INF γ express the programmed cell death-ligand 1 (PD-L1), which promotes tolerance to alloantigens via activation of Tregs [59–61], as discussed further below. Injured RTECs and renal endothelial cells also produce TGF β , a known activator of Tregs and plasmacytoid dendritic cell (pDCs) (see below) [62–64].

A commonality between the tolerance-prone kidney and liver is the extensive network of tissue-resident leukocytes present within the organ parenchyma [58,65]. The liver exhibits the highest propensity for tolerance without immunosuppression [29,66,67] and the importance of nonparenchymal cells in this observation is supported by the fact that isolated hepatocyte transplants are acutely rejected [68]. The liver plays a critical role in immune surveillance, pathogen detection, and host defense as it is constantly exposed to blood-borne pathogens, particularly via the portal vein, which drains the gut [58,69]. It contains the largest reticuloendothelial system in the body, with the largest population of resident macrophages (Kupffer cells) [58]. The liver acts as an immunological filter in that the concentration of pathogen-derived products such as lipopolysaccharide decreases by 100-fold after traveling through the liver [70]. At the same time, depletion of Kupffer cells in mice results in nearly 100% mortality after exposure to a dose of bacteria that is sublethal in wild-type mice, thus indicating that the liver is essential in immuneactivation and pathogen defense [71,72]. Additional cellular compartments that participate in antigen detection and the maintenance of hepatic immune tolerance include: liver sinusoidal endothelial cells, which are the most abundant nonparenchymal cell in the liver and serve regulatory functions via antigen presentation and cross-presentation associated with PD-L1 expression [73–75]; dendritic cells, which promote T-cell tolerance rather than activation via IL-10 [76–78]; and hepatic stellate cells (HSCs), which are discussed in detail below. Whether nonparenchymal cells in other tolerance-prone organs such as the kidney play a role in lowering the threshold for allorecognition by T cells and subsequent rejection is less well understood. However, the kidney serves a similar functional role in filtering blood and is comprised of a diverse network of nonparenchymal cells, including resident yolk-sac and bone marrow-derived macrophages and dendritic cells, lymphocytes, pericytes, and podocytes. Furthermore, in the context of systemic inflammation from sepsis, the kidney is able to undergo metabolic adaptations and reprogramming of cellular signaling to limit organ dysfunction and the progression of fibrosis to chronic kidney disease [79]. Whether similar mechanisms are activated in response to noninfectious insults such as organ transplantation and whether these mechanisms are present in other tolerance-prone organs is an important area for future study.

Renal tubule epithelial cells

RTECs represent an intriguing candidate population to mediate KICAT. IFN γ -treated human RTECs have been shown to participate in the induction of allospecific tolerance [80]. Potential mechanisms for RTEC-induced tolerance include the upregulation of programmed cell death 1 (PD-1) and indoleamine 2,3-dioxygenase (IDO) [60,81] as PD-1 signaling results in the conversion of human TH1 cells into Treg cells [82]. Indeed, Foxp3⁺ T cells are enriched in the tubules in mouse [83] and human renal allografts [84]. RTECs are also known to produce and activate TGF β [85], which is a major inducer of Foxp3 Tregs [64] and tolerogenic pDCs [62].

Dendritic cells

As mentioned earlier, conventional resident dendritic cells in the liver are thought to be mediators of liver tolerance. They can dampen inflammation after ischemia-reperfusion injury (IRI) [86,87] thus blunting T-cell responses and ultimately prolonging graft survival

[88,89] via expression of anti-inflammatory molecules such as IL-10 [90] and PD-L1 [74]. After transplantation, donor-derived dendritic cells are rapidly replaced by recipient dendritic cells, over half of which display donor MHC class I molecules on their surface. Such intercellular transfer of membrane proteins was initially recognized in immunity to viral infection and has been termed cross-dressing (XD) [91]. XD-dendritic cells are characterized by robust expression of PD-L1 and IL-10. They not only fail to stimulate alloreactive T-cells, but also they actively suppress antidonor T-cell proliferation [92[■]]. Significantly, while graft expression of PD-L1 is necessary for liver tolerance [93], XD-dendritic cells in the heart and kidney have been shown to play a different role (i.e., favor rejection) [94,95,96[■]]. These findings not only highlight the importance of tissue-resident dendritic cells in liver tolerance, but also suggest that the function of dendritic cells can be organ-specific [92[■]].

Plasmacytoid dendritic cells

pDCs represent a distinctive dendritic cell population that can act as suppressive cells when expressing the inducible tolerogenic enzyme IDO, the inducible costimulator ligand, and/or PD-L1. They can facilitate the generation of Tregs and the suppression of autoreactive and alloreactive cells, inducing tolerance to hearts in mice [97–99]. Results from our laboratory suggest that the presence of PDCA-1⁺B220⁺pDCs in DBA/2 kidneys but not hearts allografts may explain why DBA/2 kidneys are spontaneously accepted when transplanted into B6 WT recipients, whereas DBA/2 hearts are rejected (Alessandrini *et al.*, unpublished data).

Macrophages

The unique and often divergent roles of different macrophage populations within a given organ is currently a topic of intense study, but the functional consequence of these differences has not been well defined in the context of solid organ transplantation [100]. In swine, when intrapulmonary passenger leukocytes were MHC-matched to recipients, lung allograft survival was significantly higher than in nonmatched controls [101]. In the human and mouse heart, distinct macrophage populations can be identified based on the expression of CCR2. Although CCR2[−] macrophages are derived from the primitive yolk sac, entering the heart during embryonic development and are maintained by in-situ proliferation without contribution from blood or bone marrow, CCR2⁺ macrophages are generated by hematopoietic precursors and are maintained via monocyte recruitment [102–104]. These macrophage subsets also exhibit distinct functions. CCR2[−] macrophages are active in cardiac regeneration and functional recovery after injury, while CCR2⁺ macrophages are activated after IRI and propagate the postinjury inflammatory response [105[■]]. In the liver, Kupffer cells scavenge circulating antigens and present them to T-cells, which ultimately results in expansion of IL-10 producing Tregs, thus preventing local and systemic inflammation. These tolerogenic features are not characteristic of resident hepatic macrophages derived from monocytes (i.e., non-Kupffer cell macrophages), which produce a proinflammatory response when activated during systemic inflammation [106]. How individual resident macrophage subsets are affected by transplantation and whether they play a role in tolerance or rejection is an important area of future study. This is particularly true because phenotypically and functionally distinct macrophage subsets are present in all

organs, and their proliferation, activation, migration, and quantity before and after transplantation undoubtedly plays a role in the proclivity of a given organ to develop tolerance.

Hepatic stellate cells

There are other unique cell types in tolerance-prone organs that possess tolerogenic properties. In the liver, HSCs are weak antigen presenting cells that store vitamin A and have strong immunoregulatory properties through induction of T cell apoptosis, generation of myeloid-derived suppressor cells, inhibition of CD8⁺ T-cell responses and enrichment of Tregs [107]. Importantly, HSCs can confer unresponsiveness and long-term survival upon tolerance-resistant *islet* allografts by inducing Tregs [108] and myeloid-derived suppressor cells [109]. HSC cotransplantation with isolated hepatocytes also improves hepatocyte engraftment by preventing their acute rejection [110]. Whether organ-specific homologues to HSCs exist in the kidney but are absent in tolerance-resistant organs has not been studied.

Mesenchymal stem cells

Other potential intraorgan tolerogenic cells that differ in character and quantity between organs include mesenchymal stem cells (MSCs), a cell type shown to inhibit activated lymphocytes and induce the survival and activation of regulatory macrophages and T-cells [111]. Significantly, MSCs derived from different tissues have phenotypic and functional differences [111], which may contribute to organ-specific differences in the propensity to develop posttransplant tolerance. This is particularly possible because MSCs from the heart [112], lung [113], liver [114] and kidney [115] remain functional for many years posttransplant. Indeed, liver mesenchymal nonparenchymal cells have been shown to promote liver-specific tolerance by eliminating alloreactive T effector cells via expression of B7-H1, IL-10, and TGF- β as well as enhancing Tregs myeloid-derived suppressor cells [116■].

T regulatory cell-rich organized lymphoid structures

The appearance of novel FoxP3⁺Treg-rich organized lymphoid structures (TOLS) in the parenchyma of spontaneously accepted murine kidney allografts has recently been described [36]. TOLS developed as prominent lymphoid sheaths around central arterioles in accepted DBA/2 kidneys in B6.Foxp3^{DTR+/y} recipients and contained large numbers of CD3⁺Foxp3⁺Tcells (30% of T cells), pDCs, and B cells. They were distinct from tertiary lymphoid structures (TLO) found in chronic inflammation as they lacked high endothelial venules (MECA79⁺) and germinal centers and contained few CD8 cells and macrophages. Depletion of Foxp3⁺ cells led to TOLS disintegration and acute cellular rejection [36] suggesting that TOLS contribute to the tolerogenicity of kidney allografts in a fundamental way. We have also observed TOLS with abundant FoxP3⁺T cells in the kidney allografts of long-term tolerant heart/kidney NHP recipients and even in human recipients tolerant of kidney allografts. Elucidating the factors involved in the generation of TOLS and the function of these unique TLO in promoting tolerance are areas of active investigation.

CIRCULATING FACTORS

In addition, soluble factors produced by the kidney or liver such as erythropoietin (EPO), bilirubin, and vitamin D may play a role in the tolerance-prone phenotype.

Erythropoietin

Recent studies suggest that EPO, a kidney-based hormone of erythropoiesis, may also play an unanticipated role in kidney tolerance induction/maintenance. EPO can inhibit T-cell proliferation and cytokine production while augmenting murine Treg induction and stability [117]. EPO has also been shown to increase macrophage-mediated T-cell suppression *in vitro* [118]. Moreover, exogenous administration of EPO in a murine heart transplant model prolonged allograft survival while its pharmacological depletion prevented renal allograft tolerance [119]. To achieve its protolerogenic effect, EPO may have to act locally and directly on donor cells or infiltrating recipient alloreactive T cells within the renal allograft and do so in concentrations not present in physiological circulating levels. This would explain why the native kidneys that produce EPO do not dampen alloimmunity in recipients of other organs, for example, isolated heart allografts. The EPO hypothesis provides an intriguing alternative explanation for the protolerogenic phenotype of kidney allografts.

Bilirubin

Bilirubin is one of the most potent naturally occurring antioxidants [120,121]. Patient's with Gilbert's syndrome, an inborn error in bilirubin conjugation that results in elevated circulating levels of unconjugated bilirubin, have lower incidences of diabetic nephropathy, coronary artery disease, cerebral vascular disease, metabolic syndrome, and transplant rejection [122]. Along with iron and carbon monoxide, bilirubin is a byproduct of heme metabolism by the anti-inflammatory, antiapoptotic, and immunoregulatory enzyme, heme oxygenase-1 (HO-1) [123]. HO-1 is an inducible enzyme most highly expressed in organs densely populated by innate immunological cells, such as the spleen [124]. Significantly, animal studies have demonstrated that HO-1 is robustly induced in tolerance-prone organs such as the kidney and liver after injury, while its basal expression and postinjury induction is lower, but still important, in the tolerance-resistant heart. Using organ-specific and cell-specific transgenic models to reduce or amplify postinjury induction of HO-1 has demonstrated that the enzyme influences immune cell trafficking [123], polarization [125], and cytokine production [126] in a way that favors graft tolerance [127–131]. Bilirubin is partially responsible for the anti-inflammatory properties of HO-1 expression. Its antioxidant properties blunt the effects of oxidative stress induced by posttransplant inflammation and reperfusion injury [132–134,135], improve posttransplant hemodynamics by providing resistance to angiotensin II and increased bioavailability of nitric oxide [136,137], promote Treg expansion [138], and blunt expression of proinflammatory cytokines such as IL-2 [139]. Furthermore, the toleranceprone liver, and to a lesser extent, kidney, are involved in bilirubin metabolism and excretion, suggesting that this molecule, as well as the HO-1 system, may contribute to their propensity for tolerance.

Vitamin D

The kidney and liver play a vital role in vitamin D biogenesis and metabolism. Vitamin D₃ is generated in the skin and is then metabolized in the liver to 25(OH)D₃, which is converted to its active form, 1,25(OH)₂D₃ by CYP27H1 in the kidney. Given the importance of vitamin D in calcium and phosphate metabolism as well as immune function, it is not surprising that vitamin D deficiency is a significant determinant of all-cause mortality in patients with chronic kidney disease [140]. More specifically, vitamin D prevents dendritic cell maturation [141], increases IL-10 expression in dendritic cell and B cells [142], and inhibits expression of IL-2, IFN γ , and IL-17 (and thus development of TH1 and TH17 subsets) while at the same time favoring Treg production [143]. Even after transplantation, vitamin D deficiency is more prevalent in kidney transplant recipients than controls [144] and in liver transplant recipients who experience acute cellular rejection [145]. The lack of vitamin D may impair the development of allograft tolerance in these populations [146].

CONCLUSION

Attaining safe and reliably durable tolerance would transform the field of transplantation by protecting patients from detrimental effects of chronic immunosuppression and allograft rejection. Clinically and experimentally, it is recognized that different organs have specific thresholds for tolerance, achieved either spontaneously or using a variety of techniques for immunomodulation including mixed chimerism, targeted depletion strategies or short courses of immunosuppression. It is likely that the tolerogenicity of a particular organ depends on how factors intrinsic to that organ interact to shift the balance of the overall immune response towards or away from tolerance. Understanding the mechanisms that underlie these organ-specific differences in transplant tolerance has important clinical relevance. Identification and isolation of the potent protolerance factor(s) associated with liver and kidney allografts could be used to design novel tolerance protocols in clinical transplantation that would encompass all organs, even those resistant to tolerance.

Acknowledgements

None.

Financial support and sponsorship

The work was supported in part by grants from the National Institutes of Health to J.C.M. (PO1HL018646, PO1AI123086, UO1AI131470) and to G.B. (R21AI100278, R01DK115618).

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

■ of special interest

■■ of outstanding interest

1. Kawai T, Sogawa H, Boskovic S, et al. CD154 blockade for induction of mixed chimerism and prolonged renal allograft survival in nonhuman primates. *Am J Transplant* 2004; 4:1391–1398. [PubMed: 15307826]

2. Kawai T, Cosimi AB, Colvin RB, et al. Mixed allogeneic chimerism and renal allograft tolerance in cynomolgus monkeys. *Transplantation* 1995; 59:256–262. [PubMed: 7839449]
3. Kawai T, Poncelet A, Sachs DH, et al. Long-term outcome and alloantibody production in a nonmyeloablative regimen for induction of renal allograft tolerance. *Transplantation* 1999; 68:1767–1775. [PubMed: 10609955]
4. Kawai T, Cosimi AB, Spitzer TR, et al. HLA-mismatched renal transplantation without maintenance immunosuppression. *N Engl J Med* 2008; 358:353–361. [PubMed: 18216355]
5. Kawai T, Sachs DH, Sprangers B, et al. Long-term results in recipients of combined HLA-mismatched kidney and bone marrow transplantation without maintenance immunosuppression. *Am J Transplant* 2014; 14:1599–1611. [PubMed: 24903438]
6. Leventhal JR, Elliott MJ, Yolcu ES, et al. Immune reconstitution/immunocompetence in recipients of kidney plus hematopoietic stem/facilitating cell transplants. *Transplantation* 2015; 99:288–298. [PubMed: 25594553]
7. Scandling JD, Busque S, Shizuru JA, et al. Chimerism, graft survival, and withdrawal of immunosuppressive drugs in HLA matched and mismatched patients after living donor kidney and hematopoietic cell transplantation. *Am J Transplant* 2015; 15:695–704. [PubMed: 25693475]
8. Kawai T, Cosimi AB, Wee SL, et al. Effect of mixed hematopoietic chimerism on cardiac allograft survival in cynomolgus monkeys. *Transplantation* 2002; 73:1757–1764. [PubMed: 12084998]
9. Chandran S, Feng S. Current status of tolerance in kidney transplantation. *Curr Opin Nephrol Hypertens* 2016; 25:591–601. [PubMed: 27636772]
10. Massart A, Pallier A, Pascual J, et al. The DESCARTES-Nantes survey of kidney transplant recipients displaying clinical operational tolerance identifies 35 new tolerant patients and 34 almost tolerant patients. *Nephrol Dial Transplant* 2016; 31:1002–1013. [PubMed: 26763669]
11. Madariaga ML, Spencer PJ, Shanmugarajah K, et al. Effect of tolerance versus chronic immunosuppression protocols on the quality of life of kidney transplant recipients. *JCI Insight* 2016; 1:1–7.
12. Brouard S, Pallier A, Renaudin K, et al. The natural history of clinical operational tolerance after kidney transplantation through twenty-seven cases. *Am J Transplant* 2012; 12:3296–3307. [PubMed: 22974211]
13. Liu XQ, Hu ZQ, Pei YF, Tao R. Clinical operational tolerance in liver transplantation: state-of-the-art perspective and future prospects. *Hepatobiliary Pancreat Dis Int* 2013; 12:12–33. [PubMed: 23392795]
14. Alex BG, Bertolino PD, Bowen DG, McCaughan GW. Tolerance in liver transplantation. *Best Pract Res Clin Gastroenterol* 2012; 26:73–84. [PubMed: 22482527]
15. Assy N, Adams PC, Myers P, et al. A randomised controlled trial of total immunosuppression withdrawal in stable liver transplant recipients. *Gut* 2007; 56:304–306.
16. Ramos HC, Reyes J, Abu-Elmagd K, et al. Weaning of immunosuppression in long-term liver transplant recipients. *Transplantation* 1995; 59:212–217. [PubMed: 7839442]
17. Benitez C, Londono MC, Miquel R, et al. Prospective multicenter clinical trial of immunosuppressive drug withdrawal in stable adult liver transplant recipients. *Hepatology* 2013; 58:1824–1835. [PubMed: 23532679]
18. Feng S, Ekong UD, Lobritto SJ, et al. Complete immunosuppression withdrawal and subsequent allograft function among pediatric recipients of parental living donor liver transplants. *JAMA* 2012; 307:283–293. [PubMed: 22253395]
19. Chandrasekharan D, Issa F, Wood KJ. Achieving operational tolerance in transplantation: how can lessons from the clinic inform research directions? *Transpl Int* 2013; 26:576–589. [PubMed: 23517251]
20. Milton AD, Fabre JW. Massive induction of donor-type class I and class II major histocompatibility complex antigens in rejecting cardiac allografts in the rat. *J Exp Med* 1985; 161:98–112. [PubMed: 3881556]
21. Zhang Z, Zhu L, Quan D, et al. Pattern of liver, kidney, heart, and intestine allograft rejection in different mouse strain combinations. *Transplantation* 1996; 62:1267–1272. [PubMed: 8932270]
22. Bumgardner GL, Li J, Heininger MB, et al. In vivo immune response to allogeneic hepatocytes. *Transplant Proc* 1997; 29:2059–2060. [PubMed: 9193525]

23. Gelman AE, Okazaki M, Lai J, et al. CD4 T lymphocytes are not necessary for the acute rejection of vascularized mouse lung transplants. *J Immunol* 2008; 180:4754–4762. [PubMed: 18354199]
24. Madsen JC, Morris PJ, Wood KJ. Immunogenetics of heart transplantation in rodents. *Transplant Rev* 1997; 11(3(7)):141–150.
25. Russell PS, Chase CM, Colvin RB, Plate JM. Kidney transplants in mice. An analysis of the immune status of mice bearing long-term, H-2 incompatible transplants. *J Exp Med* 1978; 147:1449–1468. [PubMed: 148488]
26. Bickerstaff AA, Wang JJ, Pelletier RP, Orosz CG. The graft helps to define the character of the alloimmune response. *Transpl Immunol* 2002; 9:137–141. [PubMed: 12180821]
27. Dahmen U, Qian S, Rao AS, et al. Split tolerance induced by orthotopic liver transplantation in mice. *Transplantation* 1994; 58:1–8. [PubMed: 8036695]
28. Li W, Kuhr CS, Zheng XX, et al. New insights into mechanisms of spontaneous liver transplant tolerance: the role of Foxp3-expressing CD25 CD4 regulatory T cells. *Am J Transplant* 2008; 8:1639–1651. [PubMed: 18557727]
29. Qian S, Demetris AJ, Murase N, et al. Murine liver allograft transplantation: tolerance and donor cell chimerism. *Hepatology* 1994; 19:916–924. [PubMed: 8138266]
30. Sriwatanawongsa V, Davies HS, Calne RY. The essential roles of parenchymal tissues and passenger leukocytes in the tolerance induced by liver grafting in rats. *Nat Med* 1995; 1:428–432. [PubMed: 7585089]
31. Calne RY, Sells RA, Pena JR. Induction of immunological tolerance by porcine liver allografts. *Nature* 1969; 223:472–476. [PubMed: 4894426]
32. Pescovitz MD, Thistlethwaite JR Jr, Auchincloss H Jr, et al. Effect of class II antigen matching on renal allograft survival in miniature swine. *J Exp Med* 1984; 160:1495–1508. [PubMed: 6387036]
33. Bickerstaff AA, Wang JJ, Pelletier RP, Orosz CG. Murine renal allografts: spontaneous acceptance is associated with regulated T cell-mediated immunity. *J Immunol* 2001; 167:4821–4827. [PubMed: 11673485]
34. Cook CH, Bickerstaff AA, Wang JJ, et al. Spontaneous renal allograft acceptance associated with ‘regulatory’ dendritic cells and IDO. *J Immunol* 2008; 180:3103–3112. [PubMed: 18292533]
35. Wang C, Cordoba S, Hu M, et al. Spontaneous acceptance of mouse kidney allografts is associated with increased Foxp3 expression and differences in the B and T cell compartments. *Transpl Immunol* 2011; 24:149–156. [PubMed: 21199671]
36. Miyajima M, Chase CM, Alessandrini A, et al. Early acceptance of renal allografts in mice is dependent on foxp3(+) cells. *Am J Pathol* 2011; 178:1635–1645. [PubMed: 21435448]
37. Madsen JC, Sachs DH, Fallon JT, Weissman NJ. Cardiac allograft vasculopathy in partially inbred miniature swine. I. Time course pathology, and dependence on immune mechanisms. *J Thorac Cardiovasc Surg* 1996; 111:1230–1239. [PubMed: 8642825]
38. Madariaga ML, Michel SG, Tasaki M, et al. Induction of cardiac allograft tolerance across a full MHC barrier in miniature swine by donor kidney cotransplantation. *Am J Transplant* 2013; 13:2558–2566. [PubMed: 24033991]
39. Rosengard BR, Ojikutu CA, Guzzetta PC, et al. Induction of specific tolerance to class I disparate renal allografts in miniature swine with cyclosporine. *Transplantation* 1992; 54:490–497. [PubMed: 1412729]
40. Utsugi R, Barth RN, Lee RS, et al. Induction of transplantation tolerance with a short course of tacrolimus (FK506): I. Rapid and stable tolerance to twohaplotype fully MHC-mismatched kidney allografts in miniature swine. *Transplantation* 2001; 71:1368–1379. [PubMed: 11391221]
41. Allan JS, Wain JC, Schwarze ML, et al. Modeling chronic lung allograft rejection in miniature swine. *Transplantation* 2002; 73:447–453. [PubMed: 11884943]
42. Massicot-Fisher J, Noel P, Madsen JC. Recommendations of the NHLBI heart and lung tolerance working group. *Transplantation* 2001; 72:1467–1470. [PubMed: 11685126]
43. Madsen JC, Yamada K, Allan JS, et al. Transplantation tolerance prevents cardiac allograft vasculopathy in major histocompatibility complex class I disparate miniature swine. *Transplantation* 1998; 65:304–313. [PubMed: 9484744]

44. Madariaga ML, Michel SG, La Muraglia GM 2nd, et al. Kidney-induced cardiac allograft tolerance in miniature swine is dependent on MHC-matching of donor cardiac and renal parenchyma. *Am J Transplant* 2015; 15:1580–1590. [PubMed: 25824550]
45. Yamada K, Choo JK, Allan JS, et al. The effect of thymectomy on tolerance induction and cardiac allograft vasculopathy in a miniature swine heart/kidney transplantation model. *Transplantation* 1999; 68:485–491. [PubMed: 10480404]
46. Mezrich JD, Yamada K, Lee RS, et al. Induction of tolerance to heart transplants by simultaneous cotransplantation of donor kidneys may depend on a radiation-sensitive renal-cell population. *Transplantation* 2003; 76:625–631. [PubMed: 12973099]
47. Madariaga ML, Spencer PJ, Michel SG, et al. Effects of lung cotransplantation on cardiac allograft tolerance across a full major histocompatibility complex barrier in miniature swine. *Am J Transplant* 2016; 16:979–986. [PubMed: 26469344]
48. Yamada K, Mawulawde K, Menard MT, et al. Mechanisms of tolerance induction and prevention of cardiac allograft vasculopathy in miniature swine: the effect of augmentation of donor antigen load. *J Thorac Cardiovasc Surg* 2000; 119(4 Pt 1):709–719. [PubMed: 10733759]
49. Mezrich JD, Benjamin LC, Sachs JA, et al. Role of the thymus and kidney graft in the maintenance of tolerance to heart grafts in miniature swine. *Transplantation* 2005; 79:1663–1673. [PubMed: 15973167]
50. Wu A, Yamada K, Ierino FL, et al. Regulatory mechanism of peripheral tolerance: in vitro evidence for dominant suppression of host responses during the maintenance phase of tolerance to renal allografts in miniature swine. *Transpl Immunol* 2003; 11:367–374. [PubMed: 12967789]
51. Mezrich JD, Kesselheim JA, Johnston DR, et al. The role of regulatory cells in miniature Swine rendered tolerant to cardiac allografts by donor kidney cotransplantation. *Am J Transplant* 2003; 3:1107–1115. [PubMed: 12919090]
52. Giangrande I, Yamada K, Arn S, et al. Selective increase in CD4-positive graft-infiltrating mononuclear cells among the infiltrates in class I disparate kidney grafts undergoing rejection. *Transplantation* 1997; 63:722–728. [PubMed: 9075845]
53. Griesemer AD, Lamattina JC, Okumi M, et al. Linked suppression across an MHC-mismatched barrier in a miniature swine kidney transplantation model. *J Immunol* 2008; 181:4027–4036. [PubMed: 18768858]
54. Madariaga ML, Kreisel D, Madsen JC. Organ-specific differences in achieving tolerance. *Curr Opin Organ Transplant* 2015; 20:392–399. [PubMed: 26147678]
55. Porrett PM, Yuan X, LaRosa DF, et al. Mechanisms underlying blockade of allograft acceptance by TLR ligands. *J Immunol* 2008; 181:1692–1699. [PubMed: 18641305]
56. Witt CA, Meyers BF, Hachem RR. Pulmonary infections following lung transplantation. *Thorac Surg Clin* 2012; 22:403–412. [PubMed: 22789602]
57. Yamamoto S, Nava RG, Zhu J, et al. Cutting edge: *Pseudomonas aeruginosa* abolishes established lung transplant tolerance by stimulating B7 expression on neutrophils. *J Immunol* 2012; 189:4221–4225. [PubMed: 23018463]
58. Jenne CN, Kubes P. Immune surveillance by the liver. *Nat Immunol* 2013; 14:996–1006. [PubMed: 24048121]
59. Krupnick AS, Gelman AE, Barchet W, et al. Murine vascular endothelium activates and induces the generation of allogeneic CD4 25 Foxp3 regulatory T cells. *J Immunol* 2005; 175:6265–6270. [PubMed: 16272276]
60. Mohib K, Guan Q, Diao H, et al. Proapoptotic activity of indoleamine 2,3-dioxygenase expressed in renal tubular epithelial cells. *Am J Physiol Renal Physiol* 2007; 293:F801–F812. [PubMed: 17609291]
61. Schoop R, Wahl P, Le Hir M, et al. Suppressed T-cell activation by IFN-gamma-induced expression of PD-L1 on renal tubular epithelial cells. *Nephrol Dial Transplant* 2004; 19:2713–2720. [PubMed: 15353579]
62. Pallotta MT, Orabona C, Volpi C, et al. Indoleamine 2,3-dioxygenase is a signaling protein in long-term tolerance by dendritic cells. *Nat Immunol* 2011; 12:870–878. [PubMed: 21804557]

63. Robertson H, Wong WK, Burt AD, et al. Relationship between TGFbeta(1), intratubular CD103 positive T cells and acute renal allograft rejection. *Transplant Proc* 2001; 33:1159. [PubMed: 11267236]
64. Zheng SG. The critical role of TGF-beta1 in the development of induced Foxp3 regulatory T cells. *Int J Clin Exp Med* 2008; 1:192–202. [PubMed: 19079658]
65. Munro DAD, Hughes J. The origins and functions of tissue-resident macrophages in kidney development. *Front Physiol* 2017; 8:837. [PubMed: 29118719]
66. Calne RY, Sells RA, Pena JR, et al. Induction of immunological tolerance by porcine liver allografts. *Nature* 1969; 223:472–476. [PubMed: 4894426]
67. Kamada N, Brons G, Davies HS. Fully allogeneic liver grafting in rats induces a state of systemic nonreactivity to donor transplantation antigens. *Transplantation* 1980; 29:429–431. [PubMed: 6990572]
68. Bumgardner GL, Heininger M, Li J, et al. A functional model of hepatocyte transplantation for in vivo immunologic studies. *Transplantation* 1998; 65:53–61. [PubMed: 9448144]
69. Raichlin E, Kushwaha SS, Daly RC, et al. Combined heart and kidney transplantation provides an excellent survival and decreases risk of cardiac cellular rejection and coronary allograft vasculopathy. *Transplant Proc* 2011; 43:1871–1876. [PubMed: 21693292]
70. Lumsden AB, Henderson JM, Kutner MH. Endotoxin levels measured by a chromogenic assay in portal, hepatic and peripheral venous blood in patients with cirrhosis. *Hepatology* 1988; 8:232–236. [PubMed: 3281884]
71. Ebe Y, Hasegawa G, Takatsuka H, et al. The role of Kupffer cells and regulation of neutrophil migration into the liver by macrophage inflammatory protein-2 in primary listeriosis in mice. *Pathol Int* 1999; 49:519–532. [PubMed: 10469395]
72. Lee WY, Moriarty TJ, Wong CH, et al. An intravascular immune response to *Borrelia burgdorferi* involves Kupffer cells and iNKT cells. *Nat Immunol* 2010; 11:295–302. [PubMed: 20228796]
73. Berg M, Wingender G, Djandji D, et al. Cross-presentation of antigens from apoptotic tumor cells by liver sinusoidal endothelial cells leads to tumorspecific CD8 T cell tolerance. *Eur J Immunol* 2006; 36:2960–2970. [PubMed: 17039564]
74. Diehl L, Schurich A, Grochtmann R, et al. Tolerogenic maturation of liver sinusoidal endothelial cells promotes B7-homolog 1-dependent CD8 T cell tolerance. *Hepatology* 2008; 47:296–305. [PubMed: 17975811]
75. Limmer A, Ohl J, Wingender G, et al. Cross-presentation of oral antigens by liver sinusoidal endothelial cells leads to CD8 T cell tolerance. *Eur J Immunol* 2005; 35:2970–2981. [PubMed: 16163670]
76. Goddard S, Youster J, Morgan E, Adams DH. Interleukin-10 secretion differentiates dendritic cells from human liver and skin. *Am J Pathol* 2004; 164:511–519. [PubMed: 14742257]
77. Pillarisetty VG, Shah AB, Miller G, et al. Liver dendritic cells are less immunogenic than spleen dendritic cells because of differences in subtype composition. *J Immunol* 2004; 172:1009–1017. [PubMed: 14707074]
78. Tokita D, Sumpter TL, Raimondi G, et al. Poor allostimulatory function of liver plasmacytoid DC is associated with pro-apoptotic activity, dependent on regulatory T cells. *J Hepatol* 2008; 49:1008–1018. [PubMed: 18926588]
- 79 ■. Gomez H, Kellum JA, Ronco C. Metabolic reprogramming and tolerance during sepsis-induced AKI. *Nat Rev Nephrol* 2017; 13:143–151. [PubMed: 28090081] The article proposes a novel paradigm in which the immune response to sepsis includes a coordinated reprogramming of metabolic signaling which enables kidney cells to execute resistance and tolerance pathways, withstand injury, steer tissue repair, and promote organ recovery. The kidney's ability coordinate adaptive strategies that are organ-protective may explain the organ's propensity for tolerance.
80. Frasca L, Marelli-Berg F, Imami N, et al. Interferon-gamma-treated renal tubular epithelial cells induce allospecific tolerance. *Kidney Int* 1998; 53:679–689. [PubMed: 9507214]
81. Schoop R, Wahl P, Le HM, et al. Suppressed T-cell activation by IFN-gamma-induced expression of PD-L1 on renal tubular epithelial cells. *Nephrol Dial Transplant* 2004; 19:2713–2720. [PubMed: 15353579]

82. Amarnath S, Mangus CW, Wang JC, et al. The PDL1-PD1 axis converts human TH1 cells into regulatory T cells. *Sci Transl Med* 2011; 3:111ra20.
83. Brown K, Moxham V, Karegli J, et al. Ultra-localization of Foxp3 T cells within renal allografts shows infiltration of tubules mimicking rejection. *Am J Pathol* 2007; 171:1915–1922. [PubMed: 17991712]
84. Veronese F, Rotman S, Smith RN, et al. Pathological and clinical correlates of FOXP3 cells in renal allografts during acute rejection. *Am J Transplant* 2007; 7:914–922. [PubMed: 17286616]
85. Robertson H, Wong WK, Talbot D, et al. Tubulitis after renal transplantation: demonstration of an association between CD103 T cells, transforming growth factor beta1 expression and rejection grade. *Transplantation* 2001; 71:306–313. [PubMed: 11213078]
86. Bamboat ZM, Ocuin LM, Balachandran VP, et al. Conventional DCs reduce liver ischemia/reperfusion injury in mice via IL-10 secretion. *J Clin Invest* 2010; 120:559–569. [PubMed: 20093775]
87. Yoshida O, Kimura S, Jackson EK, et al. CD39 expression by hepatic myeloid dendritic cells attenuates inflammation in liver transplant ischemia-reperfusion injury in mice. *Hepatology* 2013; 58:2163–2175. [PubMed: 23813862]
88. Thomson AW, Knolle PA. Antigen-presenting cell function in the tolerogenic liver environment. *Nat Rev Immunol* 2010; 10:753–766. [PubMed: 20972472]
89. Yokota S, Yoshida O, Ono Y, et al. Liver transplantation in the mouse: insights into liver immunobiology, tissue injury, and allograft tolerance. *Liver Transpl* 2016; 22:536–546. [PubMed: 26709949]
90. Bamboat ZM, Stableford JA, Plitas G, et al. Human liver dendritic cells promote T cell hyporesponsiveness. *J Immunol* 2009; 182:1901–1911. [PubMed: 19201843]
91. Huang JF, Yang Y, Sepulveda H, et al. TCR-Mediated internalization of peptide-MHC complexes acquired by T cells. *Science* 1999; 286:952–954. [PubMed: 10542149]
- 92 ■ Ono Y, Perez-Gutierrez A, Nakao T, et al. Graft-infiltrating PD-L1(hi) cross-dressed dendritic cells regulate antidonor T cell responses in mouse liver transplant tolerance. *Hepatology* 2018; 67:1499–1515. [PubMed: 28921638] The study suggest that that cross-dressed dendritic cells in liver allografts play a central role in tolerance induction through the expression of programed deathligand 1 and IL-10 which may be unique to liver allografts.
93. Morita M, Joyce D, Miller C, et al. Rejection triggers liver transplant tolerance: involvement of mesenchyme-mediated immune control mechanisms in mice. *Hepatology* 2015; 62:915–931. [PubMed: 25998530]
94. Liu Q, Rojas-Canales DM, Divito SJ, et al. Donor dendritic cell-derived exosomes promote allograft-targeting immune response. *J Clin Invest* 2016; 126:2805–2820. [PubMed: 27348586]
95. Marino J, Babiker-Mohamed MH, Crosby-Bertorini P, et al. Donor exosomes rather than passenger leukocytes initiate alloreactive T cell responses after transplantation. *Sci Immunol* 2016; 1:aaf8759. [PubMed: 27942611]
- 96 ■ Smyth LA, Lechler RI, Lombardi G. Continuous acquisition of MHC: peptide complexes by recipient cells contributes to the generation of anti-graft CD8() T cell immunity. *Am J Transplant* 2017; 17:60–68. [PubMed: 27495898] The study makes the point that donor MHC-class I acquisition by recipient dendritic cells (semidirect allorecognition pathway) stimulates T-cell responses in vivo, emphasizing the need to regulate both the direct and indirect pathways to induce indefinite survival of the graft.
97. Ochando JC, Homma C, Yang Y, et al. Alloantigen-presenting plasmacytoid dendritic cells mediate tolerance to vascularized grafts. *Nat Immunol* 2006; 7:652–662. [PubMed: 16633346]
98. Abe M, Wang Z, de CA, Thomson AW. Plasmacytoid dendritic cell precursors induce allogeneic T-cell hyporesponsiveness and prolong heart graft survival. *Am J Transplant* 2005; 5:1808–1819. [PubMed: 15996227]
99. Gehrie E, Van der Touw W, Bromberg JS, Ochando JC. Plasmacytoid dendritic cells in tolerance. *Methods Mol Biol* 2011; 677:127–147. [PubMed: 20941607]
100. Demetris AJ, Murase N, Rao AS, et al. The dichotomous functions of passenger leukocytes in solid-organ transplantation. *Adv Nephrol Necker Hosp* 1995; 24:341–354. [PubMed: 7572418]

101. Madariaga ML, Michel SG, La Muraglia GM 2nd, et al. Recipient-matching of passenger leukocytes prolongs survival of donor lung allografts in miniature swine. *Transplantation* 2015; 99:1372–1378. [PubMed: 25757217]
102. Epelman S, Lavine KJ, Beaudin AE, et al. Embryonic and adult-derived resident cardiac macrophages are maintained through distinct mechanisms at steady state and during inflammation. *Immunity* 2014; 40:91–104. [PubMed: 24439267]
103. Lavine KJ, Epelman S, Uchida K, et al. Distinct macrophage lineages contribute to disparate patterns of cardiac recovery and remodeling in the neonatal and adult heart. *Proc Natl Acad Sci U S A* 2014; 111:16029–16034. [PubMed: 25349429]
104. Leid J, Carrelha J, Boukarabila H, et al. Primitive embryonic macrophages are required for coronary development and maturation. *Circ Res* 2016; 118:1498–1511. [PubMed: 27009605]
105. ■■■. Bajpai G, Schneider C, Wong N, et al. The human heart contains distinct macrophage subsets with divergent origins and functions. *Nat Med* 2018; 24:1234–1245. [PubMed: 29892064] The work demonstrates for the first time that distinct macrophage subsets with different functions are resident in human hearts. The precise phenotypic and functional characterization in this cells sets the stage for similar studies in other organs. These differences may underlie organ-specific variation in tolerance.
106. Heymann F, Peusquens J, Ludwig-Portugall I, et al. Liver inflammation abrogates immunological tolerance induced by Kupffer cells. *Hepatology* 2015; 62:279–291. [PubMed: 25810240]
107. Hsieh CC, Hung CH, Lu L, Qian S. Hepatic immune tolerance induced by hepatic stellate cells. *World J Gastroenterol* 2015; 21:11887–11892. [PubMed: 26576077]
108. Yang HR, Chou HS, Gu X, et al. Mechanistic insights into immunomodulation by hepatic stellate cells in mice: a critical role of interferon-gamma signaling. *Hepatology* 2009; 50:1981–1991. [PubMed: 19821484]
109. Chou HS, Hsieh CC, Charles R, et al. Myeloid-derived suppressor cells protect islet transplants By B7-H1 mediated enhancement of T regulatory cells. *Transplantation* 2012; 93:272–282. [PubMed: 22179405]
110. Dusabineza AC, Najimi M, van Hul N, et al. Hepatic stellate cells improve engraftment of human primary hepatocytes: a preclinical transplantation study in an animal model. *Cell Transplant* 2015; 24:2557–2571. [PubMed: 25706818]
111. Hoogduijn MJ, Betjes MG, Baan CC. Mesenchymal stromal cells for organ transplantation: different sources and unique characteristics? *Curr Opin Organ Transplant* 2014; 19:41–46. [PubMed: 24275893]
112. Hoogduijn MJ, Crop MJ, Peeters AM, et al. Donor-derived mesenchymal stem cells remain present and functional in the transplanted human heart. *Am J Transplant* 2009; 9:222–230. [PubMed: 18976299]
113. Lama VN, Smith L, Badri L, et al. Evidence for tissue-resident mesenchymal stem cells in human adult lung from studies of transplanted allografts. *J Clin Invest* 2007; 117:989–996. [PubMed: 17347686]
114. Pan Q, Fouraschen SM, Kaya FS, et al. Mobilization of hepatic mesenchymal stem cells from human liver grafts. *Liver Transpl* 2011; 17:596–609. [PubMed: 21506248]
115. Perico N, Casiraghi F, Gotti E, et al. Mesenchymal stromal cells and kidney transplantation: pretransplant infusion protects from graft dysfunction while fostering immunoregulation. *Transpl Int* 2013; 26:867–878. [PubMed: 23738760]
116. ■■■. Moris D, Lu L, Qian S. Mechanisms of liver-induced tolerance. *Curr Opin Organ Transplant* 2017; 22:71–78. [PubMed: 27984276] A comprehensive review article that describes how hepatic stellate cells orchestrate both innate immunity and adaptive immunity to build a negative network that leads to immune tolerance.
117. Cravedi P, Manrique J, Hanlon KE, et al. Immunosuppressive effects of erythropoietin on human alloreactive T cells. *J Am Soc Nephrol* 2014; 25:2003–2015. [PubMed: 24676641]
118. Wood MA, Goldman N, DePierri K, et al. Erythropoietin increases macrophage-mediated T cell suppression. *Cell Immunol* 2016; 306–307; 17–24.
119. ■■■. Purroy C, Fairchild RL, Tanaka T, et al. Erythropoietin receptor-mediated molecular crosstalk promotes T cell immunoregulation and transplant survival. *J Am Soc Nephrol* 2017; 28:2377–

2392. [PubMed: 28302753] These are the first results to demonstrate that kidney-derived, erythropoietin (EPO) can promote the generation of T regulatory cells via the induction of TGF β and that EPO treatment can prolong murine cardiac allograft survival.
120. Stocker R, Ames BN. Potential role of conjugated bilirubin and copper in the metabolism of lipid peroxides in bile. *Proc Natl Acad Sci U S A* 1987; 84:8130–8134. [PubMed: 3479781]
 121. Stocker R, Yamamoto Y, McDonagh AF, et al. Bilirubin is an antioxidant of possible physiological importance. *Science* 1987; 235:1043–1046. [PubMed: 3029864]
 122. Hull TD, Agarwal A. Bilirubin: a potential biomarker and therapeutic target for diabetic nephropathy. *Diabetes* 2014; 63:2613–2616. [PubMed: 25060893]
 123. Hull TD, Agarwal A, George JF. The mononuclear phagocyte system in homeostasis and disease: a role for heme oxygenase-1. *Antioxid Redox Signal* 2014; 20:1770–1788. [PubMed: 24147608]
 124. Lever JM, Boddu R, George JF, Agarwal A. Heme oxygenase-1 in kidney health and disease. *Antioxid Redox Signal* 2016; 25:165–183. [PubMed: 26906116]
 125. Naito Y, Takagi T, Higashimura Y. Heme oxygenase-1 and anti-inflammatory M2 macrophages. *Arch Biochem Biophys* 2014; 564:83–88. [PubMed: 25241054]
 126. Ryter SW, Choi AM. Targeting heme oxygenase-1 and carbon monoxide for therapeutic modulation of inflammation. *Transl Res* 2016; 167:7–34. [PubMed: 26166253]
 127. Nakamura K, Zhang M, Kageyama S, et al. Macrophage heme oxygenase-1-SIRT1-p53 axis regulates sterile inflammation in liver ischemia-reperfusion injury. *J Hepatol* 2017; 67:1232–1242. [PubMed: 28842295]
 128. Otterbein LE, Soares MP, Yamashita K, Bach FH. Heme oxygenase-1: unleashing the protective properties of heme. *Trends Immunol* 2003; 24:449–455. [PubMed: 12909459]
 129. Sato K, Balla J, Otterbein L, et al. Carbon monoxide generated by heme oxygenase-1 suppresses the rejection of mouse-to-rat cardiac transplants. *J Immunol* 2001; 166:4185–4194. [PubMed: 11238670]
 130. Soares MP, Lin Y, Anrather J, et al. Expression of heme oxygenase-1 can determine cardiac xenograft survival. *Nat Med* 1998; 4:1073–1077. [PubMed: 9734404]
 131. Zhao Y, Jia Y, Wang L, et al. Upregulation of heme oxygenase-1 endues immature dendritic cells with more potent and durable immunoregulatory properties and promotes engraftment in a stringent mouse cardiac allotransplant model. *Front Immunol* 2018; 9:1515. [PubMed: 30013566]
 132. Boon AC, Hawkins CL, Coombes JS, et al. Bilirubin scavenges chloramines and inhibits myeloperoxidase-induced protein/lipid oxidation in physiologically relevant hyperbilirubinemic serum. *Free Radic Biol Med* 2015; 86:259–268. [PubMed: 26057938]
 133. Boon AC, Lam AK, Gopalan V, et al. Endogenously elevated bilirubin modulates kidney function and protects from circulating oxidative stress in a rat model of adenine-induced kidney failure. *Sci Rep* 2015; 5:15482. [PubMed: 26498893]
 134. Sundararaghavan VL, Binopal S, Stec DE, et al. Bilirubin, a new therapeutic for kidney transplant? *Transplant Rev (Orlando)* 2018; 32:234–240. [PubMed: 29983261]
 135. ■■■ Kageyama S, Hirao H, Nakamura K, et al. Recipient HO-1 inducibility is essential for posttransplant hepatic HO-1 expression and graft protection: from bench-to-bedside. *Am J Transplant* 2018; doi: 10.1111/ajt.15043. [Epub ahead of print] By demonstrating the importance of posttransplant recipient heme oxygenase-1 (HO-1) phenotype in hepatic macrophage/neutrophil regulation and function, this translational study identifies recipient HO-1 inducibility as a novel biomarker of ischemic stress resistance in orthotopic liver transplantation.
 136. Vera T, Granger JP, Stec DE. Inhibition of bilirubin metabolism induces moderate hyperbilirubinemia and attenuates ANG II-dependent hypertension in mice. *Am J Physiol Regul Integr Comp Physiol* 2009; 297:R738–R743. [PubMed: 19571206]
 137. Vera T, Stec DE. Moderate hyperbilirubinemia improves renal hemodynamics in ANG II-dependent hypertension. *Am J Physiol Regul Integr Comp Physiol* 2010; 299:R1044–R1049. [PubMed: 20668235]
 138. Jangi S, Otterbein L, Robson S. The molecular basis for the immunomodulatory activities of unconjugated bilirubin. *Int J Biochem Cell Biol* 2013; 45:2843–2851. [PubMed: 24144577]

139. Haga Y, Tempero MA, Kay D, Zetterman RK. Intracellular accumulation of unconjugated bilirubin inhibits phytohemagglutinin-induced proliferation and interleukin-2 production of human lymphocytes. *Dig Dis Sci* 1996; 41: 1468–1474. [PubMed: 8689926]
140. Pilz S, Iodice S, Zittermann A, et al. Vitamin D status and mortality risk in CKD: a meta-analysis of prospective studies. *Am J Kidney Dis* 2011; 58:374–382. [PubMed: 21636193]
141. Farias AS, Spagnol GS, Bordeaux-Rego P, et al. Vitamin D3 induces IDO tolerogenic DCs and enhances Treg, reducing the severity of EAE. *CNS Neurosci Ther* 2013; 19:269–277. [PubMed: 23521914]
142. Heine G, Niesner U, Chang HD, et al. 1,25-Dihydroxyvitamin D(3) promotes IL-10 production in human B cells. *Eur J Immunol* 2008; 38:2210–2218. [PubMed: 18651709]
143. McGregor R, Li G, Penny H, et al. Vitamin D in renal transplantation – from biological mechanisms to clinical benefits. *Am J Transplant* 2014; 14:1259–1270. [PubMed: 24840071]
144. Sadlier DM, Magee CC. Prevalence of 25(OH) vitamin D (calcidiol) deficiency at time of renal transplantation: a prospective study. *Clin Transplant* 2007; 21:683–688. [PubMed: 17988259]
145. Bitetto D, Fabris C, Falletti E, et al. Vitamin D and the risk of acute allograft rejection following human liver transplantation. *Liver Int* 2010; 30:417–444. [PubMed: 19849776]
146. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. *Nat Rev Immunol* 2008; 8:685–698. [PubMed: 19172691]

KEY POINTS

- Not only does the strength of the immune response to a particular organ allograft vary with the organ transplanted but the nature of response itself, rejection versus tolerance, varies from organ-to-organ.
- Kidney and liver allografts can actively participate in the induction and maintenance of tolerance ('toleranceprone' organs), whereas heart and lung allografts are, for the most part, 'tolerance-resistant.'
- Mechanisms underlying these organ-specific differences are unclear but most likely reflect the ability of cells or cell products intrinsic to tolerance-prone organs to enhance host regulatory pathways.
- Understanding these mechanisms could contribute to the development of strategies that extend tolerance to recipients of tolerance-resistant organs.
- Successful tolerance protocols will not be directly transferable from one organ system to another thus, preclinical testing of tolerance protocols for human transplantation will have to proceed in an organ-specific manner.