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Recent Advances into the Role of Pattern Recognition Receptors in Transplantation

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Abstract

Pattern recognition receptors (PRRs) are germline-encoded sensors best characterized for their critical role in host defense. However, there is accumulating evidence that organ transplantation induces the release or display of molecular patterns of cellular injury and death that trigger PRR-mediated inflammatory responses. There are also new insights that indicate PRRs are able to distinguish between self and non-self, suggesting the existence of non-clonal mechanisms of allorecognition. Collectively, these reports have spurred considerable interest into whether PRRs or their ligands can be targeted to promote transplant survival. This review examines the mounting evidence that PRRs play in transplant-mediated inflammation. Given the large number of PRRs, we will focus on members from four families: the complement system, toll-like receptors, the formylated peptide receptor, and scavenger receptors through examining reports of their activity in experimental models of cellular and solid organ transplantation as well as in the clinical setting.

The Complement System

The complement cascade is a component of the immune system that is evolutionarily ancient, and is involved in rapidly clearing pathogens and debris from the circulation [1]. Over a period of time, it has evolved into a key component that bridges the innate and adaptive immune responses. It is a family of over 60 proteins and its components serve a multitude of roles, including being an anaphylatoxin (i.e., C3a, C5a) for leukocytes, serving as an opsonin to facilitate phagocytes to clear debris (i.e. C3b), and participating in a membrane-attack complex to lyse bacteria (i.e. C5b-9), which can assemble on bacteria

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(such as *Neisseria*) and lyse it. In the absence of regulatory proteins, uncontrolled activation of the system can also result in disruption of host cells, resulting in immune-mediated tissue damage.

The complement system has a long-standing role in ischemia-reperfusion injury (IRI) of multiple organ systems [2–4]. Different components of the cascade have been implicated, including members of the classical, alternative [5, 6], and lectin pathways [7, 8]. Certain complement proteins serve as pattern recognition molecules, notably C1q, which is a component of the classical pathway of complement activation [9–12]. Additionally, components of the lectin pathway of activation increasingly have come to be appreciated as pattern recognition molecules [13, 14]. Multiple complement proteins also provide a cross-talk pathway with other pattern recognition molecules, notably with Toll-like receptors [15–17]. As a result of these diverse roles, the complement system increasingly is seen as an important mediator of inflammatory responses to transplanted organs [18–24] and has been a longstanding therapeutic target of interest [25–30].

The central component of the complement cascade is the protein C3, which is the most abundant protein in the circulation after albumin and α2-macroglobulin [31]. While the primary source of C3 is the liver, extrahepatic production of C3 has been found to be involved in outcomes of solid organ transplantation. For example, the local production of C3 in the kidney has been shown to be important in kidney ischemia-reperfusion injury (IRI), as well as generation of an alloimmune response [32]. Renal IRI also has been known to amplify the humoral immune response [33]. Anaphylatoxins such as C3a and C5a, generated from immune cells themselves, also have the ability to modulate alloimmune responses [20, 21, 34–36]. The primary/traditional mechanism by which complement contributes to tissue injury is through the formation of the membrane attack complex (MAC, C5b-9). Additionally, sublytic MAC formation can activate the NLRP3 inflammasome, as well as intracellular NF-κB activation [37]. In a heart transplant model, this effect was also associated with activation of allogeneic CD4 T cells [38]. Finally, while IRI may be driven by activators, the contribution of the relative deficiency/downregulation of the regulators [39] also has become increasingly examined. This review focuses on the triggers of the cascade that also serve as pattern-recognition molecules and have a known association/mechanistic link with solid organ transplant outcomes.

C1q

C1q is a known pattern-recognition molecule that activates the classical pathway of the complement cascade by binding to the Fc region of antibodies (IgM, IgG) and on membrane receptors of cells, such as cC1qR/CR (calreticulin) and gC1qR/p33 [40] [41]*), and annexin A2/A5 on apoptotic cells [42]. C1q deficiency is associated with autoimmunity [40, 43], which has been shown to be mitigated by bone marrow transplantation in pre-clinical models [44, 45]. C1q can modulate CD8 responses by controlling cellular metabolism [46]. It can bind to apoptotic cells and suppress macrophage and dendritic-cell mediated Th1 and Th17 polarization [47]. It can also limit inflammasome activity in macrophages [48]. While there is a strong fundamental basis for C1q to facilitate immunoregulation, its role in solid organ transplantation is only beginning to be elucidated. In a cardiac allograft mouse model

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(BALB/c > B6), Csencstis and colleagues showed that $C1q^{-/-}$ recipients had worse acute cellular rejection compared to wild-type recipients as demonstrated by increased immune cell infiltrate in the myocardium, hemorrhage, and myocyte necrosis [11]. $C1q^{-/-}$ mice had significantly higher proportions of %CD19+ B cells, lower %CD4 T cells, and no significant differences in %CD8 T cells in the spleen, as well as no differences in donor-reactive T cell responses. Interestingly, $C1q^{-/-}$ mice had an accelerated isotype switch of donor reactive alloantibodies (IgG), IgG deposition in the allograft, and C3d deposition in the allografts, despite no C4d deposition. These observations suggest that although C1q activates the classical pathway, allograft injury may be driven by components of the lectin and alternative pathways. Whether antibody-mediated rejection is contributing to the allograft injury despite the absence of activating the classical pathway, remains to be elucidated.

Apart from the studies on C1q in autoimmunity, understanding how it facilitates tolerance has been primarily studied using a mouse minor histocompatibility (HY) model of skin graft rejection. Using this model, Baruah and colleagues demonstrated that female $C1qa^{-/-}$ mice had a higher IFN-γ producing CD8+ Teff population, and a higher IL-10 producing CD8+Teff population, compared to wild-type females, when transplanted with skin from male mice. C1q was necessary to facilitate tolerance by intranasally administered HY peptide [49]. Subsequent work from the same group [50] has suggested that this effect is specific to C1q, C3, and C4 (i.e. early components of the classical pathway), and demonstrated the redundancy of C5 in this model. C3-deficiency in this model resulted in impaired iNOS upregulation, leading to decreased T-regulatory cell induction. While these experiments were not specifically shown in $C1qa^{-/-}$ mice, the authors suggested that the classical pathway, via C3, played an important role in intranasal peptide-mediated tolerance induction via the T-regulatory cell-dendritic cell tolerogenic loop. More recently, C1q has been shown to activate Wnt signaling and promote skeletal muscle aging [51]; whether this role is applicable in senescent allografts remains to be evaluated.

Pentraxins, ficolins and collectins

In addition to C1q, other notable pattern recognition molecules in the complement system that are relevant to solid organ transplantation are pentraxins, ficolins and collectins [52]. Many of these proteins serve as triggers for different pathways of the complement cascade. A majority of the data for ficolins exists primarily in humans [53]. These are soluble oligomeric proteins containing trimeric collagen-like regions linked to fibrinogen-related domains (FReDs) that serve as pattern-recognition molecules for pathogens and dying cells, and activate the complement system. For example, they can bind to lipopolysaccharide, components of cell walls (i.e., D-fucose), and pentraxins to activate the complement system via the classical and lectin pathways. While changes in their levels have been associated with worse clinical outcomes after renal transplantation [54, 55], a majority of the experimental models have been conducted to study the role of pentraxins and collectins, not ficolins.

Pentraxins are a family of soluble proteins that can bind to multiple pathogens, as well as host surfaces (e.g., C1q, extracellular matrix proteins, leukocytes, dying cells), to activate the classical and lectin pathway [56]. Based on the length of their primary structure, they are

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classified into short- and long-chain pentraxins. C-reactive protein (CRP) and serum amyloid P (SAP) are the prototypical short-chain pentraxins, while long pentraxin-3 (PTX3, previously referred to as TSG-14, TNF-stimulated gene 14), is the prototypical long-chain pentraxin [57]. CRP and SAA are primarily synthesized by the liver, and their synthesis is augmented in the setting of pro-inflammatory stimuli, notably IL-6, resulting in their serving as acute phase reactants. PTX3, on the other hand, is produced by multiple sources, including endothelial cells, fibroblasts, lungs, heart, ovaries, thymus, and skin. Its production also is upregulated by pro-inflammatory stimuli such as TNFα and IL-1β [58]. CRP and PTX3 have been studied in the context of allograft injury, with a considerable focus on PTX3, particularly due to its interplay with C1q, among other immunomodulatory effects.

CRP is a fluid-phase pattern-recognition molecule that can bind to pathogens, as well as ligands on injured cells/tissues [59]. As an acute-phase reactant, it has a baseline level of < 5 mcg/mL in human blood, which can increase to 500 mcg/mL in the setting of an injury/infection. CRP has a cyclic pentameric structure, which facilitates its role as a pattern-recognition molecule. On one surface, its five calcium-dependent binding sites allow it to bind to its target. On its opposite surface, it is able to bind to C1q to activate the classical pathway of complement and (FcγRs) on phagocytic cells [59, 60]. Interestingly, this FcγR-facilitated interaction with macrophages can result in the synthesis and deposition of C3 at the site of injury [61]. Those investigators used human CRP transgenic mice in combination with an FcγR- or C3-deficiency in a vascular injury model to demonstrate that the neointimal thickening associated with vascular injury was dependent on FcγR, and is complement (i.e. C3)-dependent.

Interestingly, although C1q binds to CRP, and C1q itself is immunoregulatory, CRP appears to worsen tissue damage in experimental models of renal and hepatic IRI. In a series of two manuscripts, Pegues and colleagues showed that CRP worsened renal IRI by shifting the balance of kidney-infiltrating myeloid-derived suppressor cells (MDSCs) toward a suppressive phenotype [62]. Using human CRP transgenic mice in a model of warm IRI, they showed that compared to wild-type mice, these transgenic mice had worsened physiological and histological markers of renal injury and increased FcγRI expression. There were alterations in expression of macrophage activation markers; however, the specific mechanism by which CRP worsened renal IRI remained unclear. A followup study by the same group demonstrated that CRP-transgenic mice had a higher proportion of g-MDSCs ($Gr1^{+}CD11b^{+}Ly6g^{+}Ly6c^{low}$) cells in their injured kidneys, compared to wild-type mice subjected to IRI. Additionally, the depletion of these g-MDSCs using an anti-Gr1 (depleting) antibody, reduced urine albumin levels at 24 h after renal IRI in the CRP-transgenic mice. Thus, one potential mechanism of how CRP worsens IRI has been deciphered; however, how these MDSC populations are altered (i.e., receptors involved), what other factors are playing a role in CRP-mediated IRI, and what would be the optimal targets for intervention remain unanswered.

Two other studies also warrant mention. By mating transgenic (Tg)-CRP mice to two autophagy reporter mouse lines, Tg-GFP-LC3 mice (LC3) and Tg-RFP-GFP-LC3 mice (RG-LC3) respectively, Bian and colleagues reported that CRP impaired autophagic flux in vivo (measured by LC3 II/I and p62 levels by immunoblotting, GFP-LC3 punctae post-IRI

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by immunohistochemistry), ex vivo and in vitro in a warm renal IRI. CRP also impaired the dissociation of beclin-1 to bcl-2, which is required for autophagy, which was rescued by rapamycin [63]. Interestingly, Thiele and colleagues showed that a conformational change in pentameric CRP to isoforms expressing pro-inflammatory neo-epitopes was needed for inducing IRI in rat kidneys. They proposed that circulating pCRP could bind to activated biomembranes in the microcirculation of the injured tissue and be converted to bioactive pCRP (expressing neoepitopes), dissociate, and form monomeric CRP (mCRP) [64]. Those structurally altered CRP isoforms facilitated leukocyte recruitment by increasing leukocyte rolling and adhesion to endothelial cells (determined using intravital microscopy) and ROS formation in leukocytes (by activating NAPDH oxidase enzyme complex). Tested therapies for reducing that injury in their pre-clinical model system included 1,6-bis(phosphocholine)-hexane (1,6-bisPC), which stabilized pCRP and prevented the conformational changes that expose pro-inflammatory neo-epitopes, and nystatin, which reduced ROS formation in leukocytes by blocking lipid-raft dependent pathways. CRP activation, with IgM and C3 deposition has also been observed in rat hepatic IRI model, suggesting that the pro-inflammatory role of CRP in IRI may be applicable in multiple organ systems [65]. However, the specifics in each organ solid organ transplant system remain to be explored, and current knowledge is largely built upon what has been shown in renal transplant literature.

Long pentraxins are a family of proteins that have an unrelated N-terminal coupled to a pentraxin-like C terminal [8, 66]. The prototype long pentraxin, PTX3, acts as an acute-phase reactant, whose synthesis is increased by TNFα and IL-1β. Unlike short pentraxins (i.e., CRP), functionally relevant PTX3 has extrahepatic sources, including the heart, lungs, and bone marrow [8]. This local synthesis results in unique phenotypes in the context of IRI and transplantation, many of which have their basis in the biology of PTX3. Specifically, PTX3 and C1q can reciprocally bind to each other, and have different functions in the clearance of apoptotic cells. For example, while C1q is responsible for binding to apoptotic cells and facilitating their clearance by macrophages, soluble PTX3 removes bound C1q from apoptotic cells, leading to impaired complement activation on dying cells, and reduced C1q-mediated phagocytosis [67]. This would suggest PTX3 impairs recognition of self-antigens, promoting autoimmunity. If this concept was then extrapolated to IRI in the allograft tissue, PTX3-deficiency would increase the risk of alloantigen exposure, increasing the risk of allograft rejection. PTX3 also can interact with FcγRIII to facilitate clearance of apoptotic debris [68]. In the absence of this interaction, other pattern recognition molecules of the innate immune system infiltrate into the injured tissue, contributing to injury.

The concept that PTX3 limits tissue injury has been observed in models of heart and renal IRI and transplantation. While it was initially demonstrated that exogenously administered PTX3 limited cardiac injury in acute myocardial infarction [69], Zhu and colleagues more recently showed that an exogenous administration of PTX3 reduced myocardial injury after heart transplantation, and regulated the expansion of γδ T cells, the major source of IL-17A [70]. Conversely, a neutralizing antibody against PTX3 worsened cardiomyocyte apoptosis and increased the recruitment of neutrophils and macrophages. Interestingly, the local source of PTX3 that reduces cellular injury has become of increasing interest. Shimizu and colleagues used chimeric mice in a model of myocardial IRI, and found that PTX3 needed to

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be generated from bone-marrow derived cells, not tissue-resident cardiac cells, to attenuate myocardial injury via attenuating neutrophil infiltration, ROS generation and proinflammatory cytokine production (i.e., IL-6) [71].

A similar phenotype has also been observed in a renal hilar clamp model (warm IRI), wherein PTX3 was found to attenuate IRI-induced fibrosis via IL-6-STAT3 axis [72]. A different group of investigators demonstrated that the reno-protective effect of PTX3 may occur through tissue-resident (intra-renal) $CD45^{+}CD11c^{+}$cells and $CD45^{+}CD11b^{+}$ cells (and not the $CD45^{-}$ cells) by regulating neutrophil adhesion and transmigration, attenuating TNFα and IL-6 release, and tubular necrosis [73]. Those manuscripts suggested that while the immunoregulatory effects of PTX3 may not be restricted to a single organ, the source of the protective PTX3 may be unique, and recipient versus donor PTX3 sources (and levels) would need to be considered when evaluating how best to augment PTX3 levels at the site of injury. This is especially important in the context of lung transplantation; where experimental data are lacking, and the main known finding in humans is that elevated long PTX3 levels are associated with primary graft dysfunction, a consequence of lung IRI and a form of acute lung injury, in lung transplant recipients with pulmonary fibrosis. The source of PTX3 and whether it is protective or deleterious in the context of lung transplantation is an area of active investigation of our laboratory.

Similar to pentraxins, collectins also are pattern-recognition molecules used by the complement system, their name representing collagen-like lectins [74]. Of these collectins, the most commonly known lectin is mannose-binding lectin (MBL), which is primarily produced by hepatocytes. However, there are a number of collectins that are locally synthesized, and are increasingly seen to be pattern-recognition molecules that influence outcomes in organ transplantation, notably collectin-11 [75]. Surfactant proteins (i.e., SP-A and SP-D) also are collectins that serve as pattern-recognition receptors. They contain both collagen-like sequences at the N terminus and calcium-dependent lectin domains at the C terminus, and provide immunomodulatory effects specific to the lung [76–78]. Studies in humans revealed that low levels of SP-A in the donor lung prior to implantation were associated with lower survival, and that phenotype may be driven by donor SP-A2 polymorphisms [79, 80]. Those studies suggested that the effects of decreased SP-A in the lung largely affected outcomes in the first year after transplantation [80, 81]. However, given that most experimental research on the role of surfactant proteins in organ transplantation has occurred over 10 years ago [82, 83], this discussion is focused on advances in the understanding of the role of MBL and collectin-11.

Mannose-binding lectin (MBL) and MBL-associated serine proteases (MASP)

MBL is a protein consisting of O-glycosylated polypeptide chains, the basic subunit of which is a trimer, that can form a series of higher oligomers. These multimers of the triple subunit can form a three-dimensional structure similar to C1q, thus facilitating pattern recognition [74, 84]. Among the four regions on each polypeptide, the collagen-like domain interacts with enzymes known as MBL-associated serine proteases (MASPs), and can also bind to receptors such as cC1qR (calreticulin), CR1, and C1qRp on phagocytes [85]. This association with MASP allows MBL to act as an opsonin and activate the lectin pathway of

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complement. Additionally, the interaction with phagocytes can influence the cellular immune response, similar to its interaction with other pattern-recognition molecules such as pentraxins. While the liver is the primary source of MBL [86], it is also detected in other body fluids, including bronchoalveolar lavage fluid. and urine. Genetic polymorphisms considerably influence its levels in the circulation [87]. As a pattern-recognition molecule, MBL appears to regulate tissue injury in experimental models of heart, kidney, and gut IRI [88]. Specifically, mice and rats lacking MBL are protected from myocardial IRI [89–91]. One proposed mechanism for MBL-mediated IRI is that the injured endothelium binds to MBL and IgM, which results in complement activation, and can set up a cascade of events that results in NLRP3 inflammasome assembly and IL1β release [92]. In the context of murine cardiac transplantation, recipient MBL-initiated complement activation contributed to an increased proportion of donor-reactive, IFNγ-producing spleen cells, which could be targeted in the perioperative period (day 0 and 1 post-transplantation) using C1-inhibitor therapy in combination with CTLA-Ig [93].

The role of MBL-initiated allograft injury, and targeting it with C1-inhibitor therapy, also has been studied in renal transplantation. Specifically, in a swine model of renal IRI, C1-inhibitor therapy: (1) decreased tubular damage, including tubular epithelial cell death, (2) decreased peritubular capillary and glomerular complement deposition (i.e. C4d, C5b-9), and (3) decreased the number of kidney-infiltrating $CD163^+$ and T effector cells ($CD4^+$ and $CD8^+$) [94, 95]). However, there are a couple of caveats to consider in MBL-initiated allograft injury and targeting it. First, the effects of MBL may be complement-independent. Van der Pol and colleagues demonstrated that exposure of tubular epithelial cells to circulating MBL resulted in rapid internalization of MBL and tubular epithelial cell death that could not be prevented in spite of circulating C3 levels being depleted by using cobra-venom factor [95]. Second, the effect of C1-inhibitor therapy extendd beyond simply inhibiting the classical and lectin pathways of complement activation [96–98]

Among the MBL-associated serine proteases, MASP2 is the main enzyme that has been demonstrated to modify outcomes in experimental solid organ transplantation. MASP2 occurs as a single-chain polypeptide synthesized by the liver. It has domains analogous to C1r, C1s, MASP-1, and MASP-3, and undergoes calcium-dependent dimerization. It is generated as a pro-enzyme which is activated by cleavage to form a quaternary structure comprised of α- and β-chains linked by a disulfide bond. It can bind to collagen-like domains of MBL and certain ficolins and collectins, which serve as pattern-recognition molecules of the lectin pathway. As a result of these interactions, it circulates bound to these proteins, but becomes activated when it is concentrated on a target surface to cleave C2 and C4 to generate a lectin pathway convertase (C4bC2a) and activate the complement cascade. MASP2 can be either autoactivated in these settings or cleaved by MASP-1 [99]. Notably, MASP2 is the only protease of the lectin pathway that can cleave C4; thus making it critical for lectin pathway activation [100]. In addition, it can activate the cascade by bypassing C4 (due to its interactions with MASP-1 and C2 [101], and can promote clotting. Hence, this enzyme plays an important role in lectin-pathway-mediated tissue injury.

The effects of MASP-2 on tissue injury have been demonstrated in renal, cardiac and gastrointestinal IRI models. In the process of understanding whether the role of MASP2 is

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specifically through C4, Schwaeble and colleagues showed that MASP2-deficient mice had smaller infarct volumes than wild-type mice undergoing transient myocardial IRI. Both genetic MASP2 deficiency and pharmacologic abrogation of MASP2 activation, using a murine-specific MASP-2 inhibitor, AbyD 04211, also mitigated gastrointestinal IRI [101]. This approach was subsequently validated by Asgari and colleagues in a model of renal IRI in the setting of syngeneic renal transplantation, where the activity of MASP2 via its C4 bypass mechanism was identified as a contributor to delayed graft function [102].

Interestingly, MASP-2 does not appear to be an acute phase reactant. In other words, precise substrates need to be made available locally, and/or be deposited on an activated surface for MASP-2 to activate both C4-dependent and -independent mechanisms of complement cascade activation; and this activation can be therapeutically harnessed in experimental models to reduce IRI. Along those lines, Farrar and colleagues showed that L-fucose is exposed on renal tubular epithelial cells after IRI, and thats ligand binds to collectin-11 (CL-11), whose synthesis is rapidly increased in the kidney in the setting of IRI [75]. L-fucose has a known motif for binding to MASP-1, MASP-2 and MASP-3. The L-fucose-CL-11 interaction triggered MASP-2 activation, local complement activation, and tissue injury, and could be targeted using sugar-moiety specific (i.e., fucosidase) treatment, as demonstrated *in vitro*.

Toll-like receptors (TLR)

TLRs are a group of PRRs that are broadly expressed on immune cells. Their expression and function has been characterized mainly on innate immune cells such as neutrophils, monocytes, macrophages, dendritic cells, and natural killer cells [103], although they have been found to play important roles in B and T lymphocytes [104]. To date, 11 human and 13 mouse TLRs have been identified that recognize distinct pathogen-derived or endogenous ligands, all signaling through MyD88, except for TLR3. They were originally identified on innate immune cells by their ability to drive inflammatory cytokine expression and promote antigen presentation following engagement with pathogen associated molecular patterns [105, 106]. However, later work by Matzinger and colleagues [107] demonstrated that TLRs also could sense sterile cellular injury through recognition of damage-associated molecular patterns (DAMPs), which structurally resemble PAMPs (Table 2). Upon engagement, TLRs signaling is largely differentiated by the recruitment of two adaptor molecules, MyD88 and TRIF. MyD88-dependent signaling leads to the activation of the IKK complex, which results in the activation of MAP kinases and NF-κB. MyD88-independent pathways signal through TRIF, which leads to the activation of TBK1 and RIPK1 kinases. TBK1 pathways lead to IRF3 phosphorylation and Interferon type I production. RIPK1 pathways activate TAK1, leading to NFκB transcription [108]. TLR4 is the only TLR that utilizes both MyD88 and TRIF signaling pathways [109].

The importance of TLR expression in a transplant setting was first recognized by the seminal work by Goldstein and Lakkis who demonstrated that MyD88 inhibits indefinite allograft survival in a mouse model of minor antigen-mismatch skin transplantation [110]. They reasoned this was due to reduced numbers of donor DCs trafficking into draining lymph nodes resulting in impaired alloantigen-specific T cell generation. Notably, TLR-

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signaling dependent DC trafficking was later observed in a complete major and minor MHC mismatched model of mouse skin transplantation, although both MyD88 and Trif deficiency were required to extend allograft survival in this setting [111]. Later studies have largely focused on the contribution of TLR2 and TLR4 to graft survival given several DAMPs associated with solid organ injury are recognized by both TLRs. These include heat shock proteins [112, 113] and hyaluronic acid (HA) [114] [115]. Interestingly, TLR4 is a very highly cited mediator of heart [116, 117], liver [118], lung [119, 120], and kidney [121] IRI suggesting it may play a dominant role in perioperative transplant injury although it is unclear as to the identity of the cognate ligand(s) in many of these reports. However, in generating downstream adaptive immune responses to transplanted organs both TLR2 and 4 are likely both required [110]. In a model of mouse orthotopic lung transplantation, recipient double deficiency in TLR2 and 4 were necessary to inhibit low molecular weight hyaluronic acid -mediated acute rejection [122]. The same study also showed that generation of alloreactive effector T cells was sharply reduced in TLR2$^{-/-}$TLR4$^{-/-}$ recipients.

Additional insight into the role of TLRs in graft survival have been gained through studying the effects of pathogen associated molecular pattern administration to experimental transplant models pointing to the possible underlying mechanisms of infection-associated allograft rejection. For example, the co-injection of Pam3Cys, LPS, or bacterial CpG DNA oligonucleotides, respective ligands for TLR2, TLR4 and TLR9, prevented co-stimulatory blockade-mediated allograft survival by impairing the deletion of alloreactive CD8^{+} T cells in a mouse model of skin transplantation [123]. Several reports have also suggested that TLR-mediated inflammatory responses prevent tolerance through inhibiting the suppression, recruitment or stability of Foxp3+ CD4+ T regulatory (Treg) cells. Medzhitov and colleagues first demonstrated that TLR-driven IL-6 expression by dendritic cells inhibits Treg mediate-suppression of effector T cells [124]. Interestingly, CpG DNA-mediated IL-6 and IL-17 was later shown to prevent anti-CD154-mediated conversion of conventional T cells into Tregs as well as preventing mouse heart allograft tolerance [125]. However, the role of IL-6 remains controversial as others have shown in multiple experimental transplant models the existence of IL-6 independent mechanisms that impair Treg suppressive capacity in response to CpG DNA stimulation [126]. Although these effects are likely mediated by TLR9, intracellular PRRs such as STING have been shown to recognize double stranded DNA, making still unclear if targeting TLR9 would be an effective strategy at promoting Treg-mediated effects [127]. It is also likely that other TLR ligands play a role on Treg stability or recruitment. In a mouse islet transplantation model, TLR4 deficiency led to augmented rapamycin-induced Treg expansion and prolonged allograft survival [128]. Additionally, Hsieh and colleagues have demonstrated that silencing TLR4-MyD88 signaling pathway in femoral bone transplants promoted Treg expansion along with allograft survival [129].

TLR reactivity and expression patterns have also been linked to clinical outcomes after transplantation. For example, by measuring TLR reactivity in reporter cells line exposed to blood samples from liver transplant recipients, Sosa et al recently demonstrated that a positive TLR4 and 9 reactivity to the post-reperfusion samples was a major risk factor for IRI associated with orthotopic liver transplantation, especially when coupled to a negative reactivity to pre-reperfusion samples [130]. Higher levels of TLR4 and TLR2 have been

detected in patients with developing kidney graft dysfunction [131] and liver cellular rejection [132] when compared to recipients with stable transplants. Moreover, higher TLR4 expression and increased TNFα and IL-6 responses to LPS in monocytes from patients before liver transplantation also has been associated with increased risk of graft rejection [133]. Additionally, increased survival has been observed in lung recipients carrying the hyporesponsive TLR4 polymorphisms Asp299Gly or Thr399Ile [134]. Altogether, those findings suggest that either profiling TLR expression or assessing genetic TLR polymorphisms may have potential applications in predicting the risk for allograft rejection.

Although targeting TLRs may be advantageous to promote allograft survival, new work has also illuminated their importance in maintaining suppressive cell populations. For example, TLR2 and 4 stimulation has been shown to promote Treg numbers and suppressive function in the intestine following infection with *Fusobacterium nucleatum* [135]. Repeated administration of LPS was also shown to drive Treg expansion and prevent experimentally-induced allergic asthma and autoimmune diabetes [136]. Interestingly, TLR4 drives the expansion of $CD11b^{+}Gri^{int}(Ly6G^{int})F4/80^{+}$ cells, which display suppressive activity similar to myeloid derived suppressor cells (MDSCs) [137]. Several reports have demonstrated a critical role of MDSCs in promoting kidney, heart and lung transplantation tolerance [138, 139].

Finally, TLR expression by non-immune cells [140] may be helpful in protecting tissue from injury. Liang and colleagues, using a mouse model of bleomycin-induced lung injury, showed that TLR4 expression on lung epithelial cells is protective against tissue injury through stimulating NF-κβ dependent-survival pathways [141]. A subsequent study by the same group demonstrated that, upon engagement with high molecular weight HA, TLR4 signaling promoted type II alveolar epithelial cell proliferation and renewal. Thus, although TLR engagement led to immune cell activation, it may also be important in protecting parenchymal tissues from death and fibrosis [142]. Taken together, those reports suggest that TLRs are central players in linking innate and adaptive immune responses against transplanted organs. Further studies on the role of TLR-mediated regulatory mechanisms will be needed to consider the use of this approach to promote transplant tolerance.

FPR1/TLR9

FPR1 is a seven transmembrane G-protein–coupled receptor for the *N*-formyl methionine peptides, products of bacterial peptide synthesis that are well-established neutrophil chemo-attractants [143]. FPR1 also stimulates ROS generation, phagocytosis and the degranulation of oxidants and proteases from neutrophils [144]. FPR1 signaling is mediated by PI3Kγ activation that leads to calcium flux that drives neutrophil cytoskeletal reorganization and respiratory burst activity [144]. TLR9 is an intracellular receptor highly expressed in the ER of resting immune cells such as plasmacytoid dendritic cells, macrophages and B cells. Following engagement with hypomethylated CpG DNA motifs, TLR9 relocates to lysosomes where it co-localizes with MyD88 to drive signaling that promotes the expression of pro-inflammatory cytokines, including type I interferons IL-6, TNF-α, and IL-12 [145].

Although FPR1 and TLR9 play critical roles in host defense response to bacterial infection, there is increasing recognition that they play similar and complementary roles in the

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recognition of mitochondria released following necrotic cellular injury [146]. Mitochondria, likely due to their endosymbiotic origin, express N-formylated peptides and encode hypomethylated CpG DNA motifs in their genome that can be recognized by FPR1 and TLR9, respectively. Hauser and colleagues were the first to demonstrate the pathological consequences of mitochondria-derived CpG DNA (mt-DNA) and N-formylated peptide release in patients suffering from non-infectious traumatic crush injury leading to severe inflammatory respiratory syndrome (SIRS) [147]. The group observed high levels of circulating mt-DNA in SIRS patients and that mitochondrial damage associated molecular patterns (mt-DAMPs) stimulated neutrophil calcium flux and FPR1-dependent chemotaxis along with severe solid organ damage in rodents. Recently, there are several reports of high levels of circulating plasma mt-DNA in recipients of lungs [148] and kidneys [149] with perioperative graft dysfunction. Although, it has been presumed that mt-DAMPs originate from the transplanted organ, a study using an orthotopic lung transplant model in which donor lungs encoded a mitochondrial-targeted fluorescent protein showed nearly 25% of mitochondria released following IRI originated from the recipient [148]. One possible explanation for that observation is that neutrophils can release mt-DNA through the generation of neutrophil extracellular traps [150, 151]. Interestingly, NETosis has been shown to contribute to post-graft dysfunction in clinical lung transplantation and in models of lung transplantation [152, 153]. However, it remains to be determined whether neutrophil-derived mt-DNA exacerbates graft damage, as it recently has been demonstrated that mt-DNA itself can stimulate TLR9-dependent NETosis [154].

Approaches to inhibit graft injury by mitigating the effects of mt-DAMPs have focused on targeting neutrophil trafficking. In a mouse model of warm liver IRI, Honda and colleagues utilized intravital imaging to reveal that FPR1 promoted short-range neutrophil chemotaxis into areas of hepatic necrosis [155]. The group also pre-treated mouse livers with Cyclosporine H, a pharmacological inhibitor of FPR1, and demonstrated reduced neutrophil recruitment into nonperfused hepatic tissue and attenuated IRI. Consistent with those observations, in a orthotopic mouse lung transplant model, FPR1 was shown to direct neutrophil trafficking into airspaces, resulting in exacerbation of IRI. Additionally, graft-infiltrating FPR1$^{-/-}$ neutrophils were found to have engulfed fewer donor-derived Mt-DAMPs and produced lower levels of reactive oxygenation species [148]. Nevertheless, further work will be needed to determine if targeting PRRs that recognize mt-DAMPs is viable strategy to prevent graft injury. Additionally, it remains unknown whether either FPR1 or TLR9 contributes to adaptive immune responses against allografts.

Scavenger Receptors

The innate immune system recognizes molecular patterns that allow for the differentiation between healthy and dying host cells. Mononuclear phagocytes are actively inhibited from engulfing healthy cells via repulsive signals, which can be lost from the cell surface or attenuate their avidity during cell injury or apoptosis. Interestingly, recent work has shown that gene encoded variation in scavenger receptors can result in the abrogation or altered engagement of ‘don’t eat me’ signals, resulting in the recognition of non-self. Patterns associated with death also can be utilized by the innate immune system to acquire alloantigens or inhibit inflammatory responses by APCs.

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Signal regulatory protein α (SIRPα)

Signal regulatory protein α (also known as SIRPα, CD172a, SHPS-1) is a transmembrane glycoprotein expressed mainly by myeloid cells, neurons, and stem cells. Although originally described as an inhibitor of growth factor signaling [156], SIRPα was later shown to prevent macrophage phagocytosis of healthy host cells [157]. Negative regulation of phagocytosis is accomplished by two cytoplasmic immunoreceptor tyrosine inhibitory motifs which, when phosphorylated in response to ligand engagement, trigger the recruitment of src homology phosphatases that act to block the remodeling actin cytoskeleton required for phagocytic activity [158, 159]. SIRPα binds to the broadly expressed integrin CD47. During apoptosis, CD47 changes its cell surface localization from a punctate to diffuse distribution, which in turn decreases its avidity for SIRPα, resulting in the attenuation of repulsive signals that prevent phagocytic clearance [160].

Early studies analyzing macrophage phagocytosis of red blood cells and peripheral blood mononuclear cells isolated from discordant vertebrate species suggested that phylogenetically encoded differences in SIRPα direct self-recognition [161–163]. Those findings were later reflected in positional genetics studies utilizing the non-obese diabetic (NOD)-severe combined deficiency (SCID) xenotransplantation model [164]. NOD.SCID mice are commonly used for human hematopoietic stem cell (HSC) studies due to the ability of human HSCs to self-renew and differentiate on this background. NOD SIRPα demonstrated a strong affinity for human CD47, while SIRPα from other strains were found to be poor binders of human CD47 and could not support HSC engraftment. Additionally, it was later observed that pig HSCs engineered to express human CD47 (huCD47) engrafted efficiently into NOD mice [165].

SIRPα also has been implicated recently in the control of the survival of solid organ xenotransplants. Baboon SIRPα is known to recognize huCD47. In a mixed chimerism model, pig skin grafted onto baboons was sharply prolonged by the administration of huCD47^{+} HSCs [166]. Also, huCD47 expressed on pig lung xenografts prolonged survival in baboons [167], which was later shown to be further extended by preconditioning with huCD47+ pig bone marrow transplants [168]. Perhaps the most surprising finding is that SIRPα may also play a role in alloimmune responses. Using a mouse bone marrow plug transplantation model and positional cloning techniques, Lakkis and colleagues reported that donor SIRPα amino acid polymorphisms can serve as markers of non-self [169]. Interestingly, most amino acid variability within SIRPα mouse locus was within the extracellular region and was particularly prevalent in CD47-binding immunoglobulin-like variable domain. The importance of this observation was underscored by greater binding of CD47 to allelic variants of SIRPα that promoted monocyte proliferation and monocyte-derived dendritic cell generation within bone marrow plug allografts. The authors hypothesized that innate allorecognition occurred when donor SIRPα had a greater affinity for CD47 when compared to recipient SIRPα. Although SIRPα polymorphisms also exist in humans [164], it remains to be determined if such differences control clinical transplantation outcomes.

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CD200

CD200 (also known as OX-2) is a member of the immunoglobulin superfamily primarily expressed in many cell types, including antigen presenting cells. During apoptosis, CD200 expression is upregulated through p53- and caspase-dependent pathways and reduces tissue injury and inflammatory cytokine expression [170]. The immunomodulatory effects of CD200 are mediated through its interaction with CD200R, expressed mainly by myeloid-derived APCs and activated T cells [171, 172]. CD200-deficient mice are reported to have elevated steady-state APC activation and higher susceptibility to collagen-induced arthritis and experimental autoimmune encephalitis, suggesting a critical role for this pathway in immune homeostasis [173]. In the transplant setting, early work with CD200 F_c fusion protein was shown to increase mouse skin and kidney allograft survival, and attenuate the production of antibodies to sheep red blood cell erythrocytes, indicating that CD200:CD200R signaling regulated both allo- and xenogeneic responses [174]. The effects of blocking CD200 appear to be mediated by blocking T_h1 cytokine production and inducing regulatory $CD4^+$ T cell expansion by conventional allostimulatory dendritic cells [175, 176]. Recent work with overexpression of human CD200 porcine endothelial cells (PEC) has indicated its possible use in preventing xenograft rejection in humans [177]. Overexpression of CD200 in PECs suppressed inflammatory responses by human macrophages, including TNFα, IL-1β and IL-6 expression, and improved the survival of PEC xenografts in NOD.SCID mice.

CD36

CD36 is a widely expressed transmembrane glycoprotein scavenger receptor that serves many functions in lipid metabolism and signaling. It is a well-established mediator apoptotic cell clearance through helping recognition of oxidized phosphatidyl serine, a lipid marker of cellular senescence [178, 179]. CD36 on dendritic cells promotes cross-presentation of antigens from apoptotic cells to cytotoxic cells, suggesting that CD36 promotes alloreactivity by presenting antigen derived from phagocytized apoptotic graft cells [180]. However, recent evidence suggests CD36 expression on dendritic cells may also have regulatory effects. Work conducted by Hsieh and colleagues, using a mouse allogeneic bone marrow transplant model, demonstrated that CD36 facilitated the transfer of intact MHC:peptide complexes from apoptotic bodies released by thymic epithelial cells to CD8a+ dendritic cells, which in turn altered the thymic regulatory T cell repertoire [181]. They also observed decreases in CD8a+ dendritic cells and CD36 expression in the peripheral blood of human bone marrow recipients with graft-versus host disease.

TAMs

TAMs are a distinct group of tyrosine receptor kinases found on APCs that derive their name from three family members - Tyro3, Axl, and Mer. TAMs promote efferocytosis, a phagocytotic process that facilitates the removal of dying cells. TAMs interact with the TAM ligands growth arrest-specific gene 6 protein [182] and Protein S [183], that in turn recognize phosphatidyl serine [184]. TAM engagement promotes the clearance of dying cells through a poorly described signaling pathway that results in protein kinase C activation, which stimulates actin cytoskeleton remodeling necessary for phagocytosis [185].

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TAMs also help resolve inflammation through complexing with the type I interferon receptor, which results in the attenuation of type I interferon and TLR-induced inflammatory cytokine production through driving the expression of suppressor of cytokine signaling 1 and 3 (SOCS1, SOCS3) [186]. Consistent with these observations is the profound dysregulation of immune responses and loss of self-tolerance in mice deficient in one or multiple TAMs [187, 188]. Infusion of apoptotic donor cells into murine models of islet [189] and heart [190] transplantation has suggested the importance of efferocytosis in regulating transplantation tolerance. These observations may also extend to the clinic. Extracorporeal photopheresis (ECP) is an FDA approved immunosuppressive therapy that utilizes ultraviolet A light–activated 8-methoxypsoralen-treated autologous leukocytes that are reinfused into a patient. ECP has been used to treat GVHD [191] and bronchiolitis obliterans syndrome [192], a form of chronic rejection in lung transplant recipients. The ECP treatment produces apoptotic cells, which are thought to drive some of its immunomodulatory effects [193]. Moreover, single infusions of autologous apoptotic mononuclear cells into patients with GVHD have been reported to inhibit dendritic cell maturation following challenge with LPS [194]. However, whether specific TAMs are involved in promoting allograft tolerance has only recently been investigated. Thorpe and colleagues demonstrated that the TAM Mer (MerTK) is required for mouse cardiac allograft tolerance driven by the infusion of donor apoptotic splenocytes [195].

Concluding Remarks

The transplantation of an organ into a host can be recognized by germline encoded PRRs that are stimulated by molecular patterns released or presented by injured tissue. Recent work has also supported the notion that PRRs may also recognize xeno- or allotypic differences, due to PRR polymorphisms that are present across phylogeny or within individuals of the same species. Resulting PRR engagement leads to the signaling pathways that drive the upregulation of inflammatory cytokines and antigen presentation molecules that promote adaptive immune responses against organs, ultimately leading to rejection. The selective targeting of PRRs could lead to the development of promising new therapies to promote immune tolerance.

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Table 1.

Key recent experimental models in organ transplantation involving the complement proteins that serve as soluble pattern-recognition receptors (PRRs).

PRR	Ligand	Organ	Injury
C1q	Fc region of IgM, IgG Annexin A2, A5 Membrane receptors on cells (e.g., calreticulin)	Heart	Protects against acute rejection by diminishing the humoral response [11]
		Skin	Protects against chronic rejection [49] [50]
C-reactive protein (CRP)	C1q, phosphocholine, modified LDL, certain polycations, extracellular matrix proteins (e.g., fibronectin)	Kidney	Worsens IRI [62] [63] [64]
		Liver	Associated with worse IRI [65]
Pentraxin-3 (PTX3)	C1q, growth factors (i.e., FGF2), extracellular matrix components (i.e. TSG-6), late apoptotic cells, pathogens, endothelial cells, leukocytes	Intestine	Worsens IRI [196]
		Heart	Cardioprotective role in IRI [70] [71]
		Kidney	Protective role in IRI [72, 73]
Mannose-binding lectin (MBL)	Bacterial carbohydrate motifs, Fc region of bound immunoglobulin molecules	Heart	- Worsens IRI [89] [90] [91] - Accelerates chronic allograft loss post-cold ischemia [93]
		Kidney	Worsens IRI [197] [94] [95] [198]
		Gut	Worsens IRI [199]
MBL-associated serine protease-2 (MASP2)	Enzyme binding to MBL	Kidney	Worsens DGF [102]
		Heart	Worsens IRI [101]
		Gut	Worsens IRI [101]
Collectin-11 (CL-11)	L-fucose	Kidney	Worsens IRI [75]
Surfactant protein A (SP-A)	Wide range of microorganisms and apoptotic cells *via* receptors (i.e., TLR4, C1qR, SIRPα)	Lung	- Reduces IRI in rats [82] [83]

Abbreviations: FGF2: fibroblast growth factor-2; IRI: ischemia-reperfusion injury; LDL: lowdensity lipoprotein; SIRP-α: Signal regulatory protein α; TLR4: Toll-like receptor 4; TSG-6: TNF-stimulated gene 6 protein

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Table 2.

Key recent experimental models in organ transplantation involving Toll-like receptors (TLR).

Pattern Recognition Molecule	Ligand	Target Organ	Injury
TLR2	HMGB1 Heat shock protein Hyaluronan	Skin	-Shortens allograft survival time via MyD88 signaling and enhancing Th1 responses [110] -Abrogates the effect of costimulatory blockade by preventing alloreactive CD8+ T cell apoptosis [123]
		Heart	-worsens IRI [117]
TLR4	HMGB1 Heat shock protein Hyaluronan Fibronectin Heparan sulfate	Skin	- Abrogates the effect of costimulatory blockade by preventing alloreactive CD8+ T cell apoptosis [123]
		Kidney	- TLR4 signaling by tubular epithelial cells worsens IRI [121]
		Heart	- Worsens myocardial IRI [116]
		Lung	- worsens IRI [119, 120]
		Liver	- Worsens IRI via IRF3-dependent pathway [118]
TLR9	Mitochondrial DNA HMGB1	Liver	- worsens IRI [200]
		Kidney	- worsens IRI [201]
		Heart	- worsens IRI [202]
		Lung	-- Promotes NET formation in primary graft dysfunction post-IRI [154]
FPR1	Formylated Peptides	Liver	- Promotes necrotaxis and exacerbates IRI [155]
		Lung	- Promotes airway neutrophilia and exacerbates IRI [148]
		Heart	- Increases inflammation, cardiomyocyte apoptosis and ventricular remodeling post IRI [203]

Abbreviations: HMGB1: High Mobility Group Box 1; IRI: ischemia-reperfusion injury; NET: neutrophil extracellular traps; TLR: Toll-like receptor

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Table 3.

Key recent experimental models in organ transplantation involving scavenger receptors.

Pattern Recognition Molecule	Ligand	Target Organ	Injury
SIRPα	CD47 (broadly expressed)s	Skin	- Pig skin grafted onto baboons sharply prolonged by the administration of pig huCD47+ HSCs (mixed chimerism model) [166]. - huCD47 expressed on pig lung xenografts prolonged survival in baboons [167], which could be further extended by preconditioning baboon recipients with pig bone marrow transplants bearing huCD47 [168].
		Bone marrow	- Greater binding of CD47 to allelic variants of Sirp1a promoted monocyte proliferation and monocyte-derived dendritic cell generation within bone marrow plug allografts [169].
CD200	CD200R (myeloid-derived APCs and activated T cells)	Skin	- Treatment with CD200 Fc fusion protein increases mouse skin allograft survival [174].
		Kidney	- Treatment with CD200 Fc fusion protein increases mouse kidney allograft survival [174].
		Xenografts	- Overexpression of CD200 in porcine endothelial cells (PEC) suppressed inflammatory responses by human macrophages (i.e., TNFα, IL-1β and IL-6), and improved survival of PEC xenografts in NOD.SCID mice. [177].
CD36	Oxidized phosphatidyl serine	Bone marrow	- CD36 facilitates allotolerance by the transfer of intact MHC:peptide complexes from apoptotic bodies released by thymic epithelial cells to CD8a + dendritic cells, which in turn altered the thymic regulatory T cell repertoire [181].
MerTK	Protein S, Gas6	Heart	- Facilitates tolerance driven by the infusion of donor apoptotic splenocytes [195].

Abbreviations: APC: antigen-presenting cells; MHC: major histocompatibility complex