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The Multiple Facets of Toll-like Receptors in Transplantation Biology

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Abstract

Toll-like receptors (TLRs) belong to a family of pattern-recognition receptors for microbial products and endogenous molecules released by stressed cells. Experimental studies show that TLRs are involved in the process of acute allograft rejection and that their activation can prevent transplantation tolerance. Herein, we review the expression of TLRs and the impact of TLR signaling in different cell types in grafted organs including APCs, T and B lymphocytes, epithelial and endothelial cells. We then discuss the involvement of TLRs in the different phases of the rejection phenomenon and the impact of TLR-mediated events on regulatory circuits which dampen alloimmune responses.

Keywords

Toll-like receptors; ischemia-reperfusion; acute rejection; T cells

INTRODUCTION

Toll was discovered in *Drosophila* as an essential receptor to fight fungal infection (1). Rapidly after its discovery, a mammalian equivalent of Toll (TLR4) was identified as an important inducer of inflammatory genes (2). In humans, 10 TLRs have been characterized. TLRs 1,2,4,5,6,10 are expressed at the cell membrane and recognize bacterial, fungal and parasite-derived ligands whereas TLRs 3,7,8 and 9 are present in endosomes and recognize viral and bacterial RNA and DNA (3). Interestingly, TLR2 and TLR4 can also be engaged by endogenous ligands released by damaged cells including heat shock proteins (HSPs), high mobility group box chromosomal protein 1 (HMGB1), heparan sulphate, hyaluronan fragments and fibronectin (4, 5). Therefore, TLRs represent essential sensors of “danger” and a critical link between innate and adaptive immunity (3). Most TLRs except TLR3 are coupled to the MyD88 adaptor protein which initiates a signaling cascade culminating in

activation of the NF- κ B transcription factor and of the mitogen-activated protein kinases (MAPKs) extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase (JNK), which contribute synergistically to the induction of several inflammatory genes (6). TLR3 and TLR4 signal via the TIR-containing adaptor inducing interferon (IFN)- β (TRIF) adaptor protein leading to activation of the transcription factor IFN regulatory factor (IRF) 3, which is required for the synthesis of IFN- β , the p35 chain of interleukin (IL)-12p70 and the p28 chain of IL-27 (7–9). The TLR signaling pathways are tightly regulated by several mechanisms that control the magnitude of TLR-mediated inflammation [reviewed in (10)]. The negative regulation of TLR signaling is involved in the well known phenomenon of endotoxin tolerance which is responsible for blunted responses to bacterial lipopolysaccharide (LPS) challenge in animals previously exposed to this agent (11).

Beside their role during infections, there is evidence that TLRs are also involved in a variety of disorders including autoimmune diseases - especially systemic lupus erythematosus -, atherosclerosis and bronchial asthma [reviewed in (12)]. Although TLR signaling usually contributes to pathology by eliciting inflammation, there is evidence that TLR engagement may be involved in immunosuppression in sepsis and also in protection against allergic disease in early life (12). Likewise, TLRs could play multiple roles in transplantation. While they were clearly shown to facilitate and sometimes even to be required for allograft rejection (13), we will also discuss herein the possibility that under certain settings TLR signaling may actually prolong allograft survival.

EXPRESSION OF TLRs ON IMMUNE CELLS AND PARENCHYMAL CELLS

TLRs are widely distributed and differentially expressed in various mammalian cell types and tissues (Table I) with several species-specific differences (14). TLRs are present on macrophages, dendritic cells, polymorphonuclear cells, and mast cells as well as on cells of the adaptive immune system, namely T and B cells. These cells all have characteristic TLR expression patterns which can direct their specific behavior. Monocytes, macrophages and granulocytes express most TLR family members. TLRs on macrophages and dendritic cells are needed for the upregulation of particular cytokines, MHC molecules and costimulatory molecules, are essential for phagocytosis and crucial for monitoring invading pathogens (15, 16). On neutrophils, TLRs, and particularly TLR2 and TLR4, can directly regulate migration, apoptosis and major pro-inflammatory and host defense functions (17). In addition, TLRs 2,3,5 and 9 on T cells are used as costimulatory receptors to increase proliferation/survival and/or cytokine production of TCR-stimulated T cells (18–21). In contrast, TLRs 1,2, and 4–8 are expressed by regulatory T cells (Tregs) and can modulate their suppressive phenotype resulting in increased or dampened regulatory functions (22–26). Others have reported that B cells express all TLR family members. Significant expression is however only found for TLR1 and TLRs 6–10. TLR engagement on B cells can induce and/or costimulate these cells to proliferate, and undergo class switching and differentiation into antibody-secreting cells (27, 28).

Recent observations demonstrate that TLRs are also expressed on epithelial and endothelial cells as well as on mesenchymal cells of various organs and tissues such as kidney, heart, lung, liver, skin, brain, and intestine (Table I). The role of these parenchymal-associated

TLRs is however not fully known and subject of intensive current research. Several studies suggest that parenchymal cells expressing TLRs play a crucial role in the initiation and modulation of the local immune response (29–31). Differential TLR expression is particularly apparent on epithelial cells. TLR11 is for example expressed in mouse kidney epithelium and bladder urothelium where it prevents infection by uropathogenic bacteria (32), while TLRs 2,3,4 and 5 have specific roles in bronchial and gastrointestinal epithelial defense (33–37). TLR expression was also found in other parenchymal cells of various organs. For instance, cardiomyocytes express TLRs 2,3,4,6,7,8 and 9 (cell line) whereas TLRs 1 and 5 are not expressed (38–40). Renal tubular epithelial cells express TLRs 1,2,3,4,6 and 11 but neither TLR5 nor TLR9 (41, 42). Insulin-secreting β cells in pancreatic islets were shown to express TLRs 2,4 (43) and TLR3, the latter contributing to NF- κ B-dependent β -cell apoptosis upon exposure to dsRNA (44). Thus, cell types of both hematopoietic and parenchymal origin have distinct TLR expression patterns with specific biological consequences that may play important roles in transplant biology. For instance, TLR2 is highly expressed in both parenchymal cells and infiltrating leukocytes in transplanted kidneys undergoing acute allograft rejection (Figure 1).

TLRs IN ISCHEMIA-REPERFUSION INJURY

Ischemia-reperfusion injury (IRI) is a major cause of delayed allograft function and is also an important inducer of acute and chronic transplant rejection. During the ischemia-reperfusion period, a sequence of cellular and biochemical events is initiated that can lead to cellular dysfunction and ultimately cell death. Increasing evidence suggests that endogenous and exogenous ligands are released during IRI that can activate TLRs, which in turn, initiate innate immunity and direct adaptive immune responses. In the past few years, several studies have specifically examined the expression and role of TLR2 and TLR4 in several organs subjected to IRI. TLR4-dependent signals in mice seem to promote IRI injury of at least heart, liver, kidney and lung. Indeed, TLR4-deficient mice are protected against IRI injury for up to 2h (45) and 24h (46) after reperfusion. In these animals, the amount of pro-inflammatory cytokines and the number of leukocytes are reduced following reperfusion, whereas neutrophil function is preserved (46). In line with these findings, others have observed that absence of TLR4 or of the NF- κ B subunit p50 protected mice against myocardial IRI (47, 48). TLR4 deficiency also markedly reduced inflammation and hepatocellular damage in a mouse model of hepatic IRI, whereas injury remained unchanged in MyD88-deficient mice (49). Using TLR4 chimeric mice, Tsung and colleagues showed that the effect of TLR4 on hepatic IRI and inflammation is mediated by TLR4-expressing phagocytic non-parenchymal cells such as Kupffer cells (50). Inhibition of high mobility group box 1 (HMGB1) protein, which acts as a TLR4 agonist, significantly decreased liver damage of mice subjected to ischemia-reperfusion (51, 52). TLR4 mediates IRI in kidney and lungs as well, by promoting leukocyte accumulation and the production of pro-inflammatory cytokines/chemokines (31, 53). While most of these studies focus on TLR4, TLR2 has also been shown to play a crucial role in the pathogenesis of IRI. We found that TLR2 on renal parenchyma is an important player in the initiation of exaggerated inflammation leading to renal failure following ischemia-reperfusion in mice (30). TLR2-deficient and kidney-TLR2-deficient mice (generated by reciprocal bone marrow

transplantation) displayed reduced cytokine/chemokine production, reduced leukocyte infiltration and less severe renal damage and dysfunction compared to controls (30). These data were later confirmed by Shigeoka and colleagues (54). Interestingly, blockade of TLR2 with anti-sense RNA treatment resulted in reduced renal inflammation and dysfunction after IRI (30). In contrast, TLR2-deficient mice subjected to hepatic IRI did not exhibit such protection (55) despite TLR2 expression in many hepatic cells (see Table I), indicating different roles for distinct TLRs in different organs.

TLRs IN THE INITIATION OF ALLOGRAFT REJECTION

The contribution of TLR-dependent signals to allograft rejection was first demonstrated using mice deficient in MyD88 (56, 57). Lack of MyD88 in donor and recipient mice resulted in the acceptance of skin transplants bearing minor mismatches, and in prolonged survival of fully allogeneic skin and cardiac allografts (56, 57). The only known non-TLR receptors utilizing the MyD88 pathway are IL-1R and IL-18R. However, IL-1 β -converting enzyme-deficient mice that lack IL-1R and IL-18R signaling did not display increased allograft survival, implicating a contribution by TLR signals to acute allograft rejection (56, 57). More recently, combined MyD88- and TRIF-deficiency in the donor only was also reported to delay rejection of major and minor histocompatibility antigen-mismatched allografts (58).

Several pieces of evidence suggest that TLR signals concomitant to TCR engagement can enhance the priming/survival of alloreactive T cells. TLR engagement after skin transplantation was shown to promote migration of alloantigen-expressing DCs to draining lymphoid organs (56, 58) where T cell activation is thought to occur. In a model of cardiac allograft acceptance mediated by anti-CD154 that depends on inhibition of CD4⁺ T cells and recruitment of Tregs to cardiac allografts (59), administration of the TLR9 agonist CpG or of the TLR2 ligand Pam₃CysK₄ at the time of transplantation resulted in increased production of IFN- γ by alloantigen-stimulated splenocytes and impaired intra-graft Treg recruitment (60), suggesting enhanced T cell priming and reduced regulation. In a skin graft model in which tolerance driven by anti-CD154+donor-specific transfusion depends on clonal deletion of alloreactive CD8⁺ T cells, peri-operative injection of ligands of TLR9 (CpG), TLR4 (LPS) or TLR3 (poly I:C) resulted in diminished deletion of graft-reactive CD8⁺ T cells (61), indicating TLR-dependent augmented T cell survival. In both systems, TLR engagement at the time of transplantation effectively prevented the induction of transplantation tolerance (60, 61). Interestingly, the ability of LPS and poly I:C to prevent skin allograft acceptance was dependent on their induction of type I IFN (62). This fits well with anecdotal clinical reports showing that transplanted patients treated with IFN- α for hepatitis C infection sometimes develop acute rejection of liver or kidney allografts (63–65).

If TLR-mediated signals can help initiate acute allograft rejection, what are the TLR ligands that may engage these receptors at the time of transplantation in the clinic? Endotoxin translocation has been detected early following clinical liver transplantation (66). Bacterial translocation has been evidenced after intestinal transplantation in humans, especially in grafts containing colon segments and in those exposed to prolonged cold-ischemia times (67). Interestingly, bacterial translocation was not only shown to occur after episodes of

acute rejection that may damage intestinal integrity, but also to precede acute rejection in many cases (67), suggesting that, similarly to injection of TLR agonists, TLR ligands from circulating micro-organisms may engage TLRs, promote enhanced alloresponses and precipitate acute rejection episodes in the clinic. Consistent with this hypothesis, experimental and clinical evidence demonstrate that skin, small bowel and lung, the 3 organs colonized with commensal bacteria, are the tissues most subject to acute rejection and most difficult to tolerize (60). This has led our group to propose that the increased immunogenicity of those organs is due to the translocation of commensal bacteria and/or acquired pathogenic bacteria, resulting in augmented alloimmune responses (60). Via engagement of TLRs and other microbial-sensing receptors, bacterial translocation may result in activation of donor and recipient antigen-presenting cells (APCs) leading to an increased capacity to present antigen and costimulate alloreactive T cells, rendering T cells more resistant to immunosuppressive therapies. In support of this hypothesis, we and others have shown that inhibition of TLR signaling in both donor and recipient mice results in acceptance of fully allogeneic skin allografts in animals treated with a costimulation-targeting regimen that fails to induce skin graft acceptance in wild-type recipients (60, 68). Nevertheless, bacterial translocation following organ or tissue transplantation remains to be formally demonstrated and quantified.

Aside from being augmented by microbial TLR ligands, alloimmune responses may also be enhanced by endogenous TLR agonists induced by surgical stress and IRI at the time of transplantation. As mentioned earlier, an increasing list is emerging of endogenous TLR ligands derived from apoptotic cells, heat shock proteins and degradation products of extracellular proteins (69). Hyaluronan fragments have been detected in murine skin and human lung allografts (70) and increased stimulation of alloreactive T cells by hyaluronan-activated DCs was shown to depend on the TLR2/4 adaptor TIR but not on MyD88 or TRIF (70).

TLRs IN THE EFFECTOR PHASE OF ALLOGRAFT REJECTION

In addition to augmenting the priming of alloimmune responses and facilitating the initiation of the rejection process, TLR engagement may also promote the effector phase of the rejection process. This is exemplified in an elegant murine model of bone marrow transplantation. In this model, transfer of donor T cells results in the rapid elimination of recipient hematopoietic cells but does not trigger tissue-based graft versus host disease (GVHD) in the absence of additional treatment. However, cutaneous administration of the TLR7 agonist imiquimod results in skin infiltration by donor T cells and development of skin GVHD (71), suggesting that TLR signals enable the effector phase of the alloimmune response. Similar results have recently been reported in a skin graft model in which a neoantigen is expressed by somatic but not hematopoietic cells of the graft (72). Transient T cell depletion of recipient mice permits the permanent acceptance of these healed-in skin grafts even when T cell numbers recover sufficiently to reject a freshly placed allograft. TLR7 activation within the healed-in graft resulted in its rejection but not that of contralateral untreated grafts (72), demonstrating dramatic effects by TLR signaling on immune responses at the target tissue site. Tissue-limited TLR effects were also demonstrated in the lung in another murine bone marrow transplant model. Aerosolized administration of LPS

resulted in lung GVHD lesions similar to lymphocytic bronchiolitis and obliterative bronchiolitis in a manner dependent on TLR4 expression by donor-derived hematopoietic cells (73). All three reports suggest a role of local inflammation for the recruitment of alloreactive cells to target tissues. This migration of previously primed T cells enables the effector arm of the rejection process. Whether TLR signals at target tissues promote only migration of alloreactive T cells or also enhance their effector function on a per cell basis remains to be demonstrated. Thus, lung, skin and small bowel allografts may be more immunogenic than sterile organs not only because of bacterial translocation at the time of transplantation that can enhance priming/survival of alloreactive T cells, but also because their exposure to the outside world renders them more susceptible to local microbial colonization at later time points possibly driving T cell recruitment and/or effector function. These concepts are supported by occasional reports demonstrating that infections occurring late after transplantation can precipitate episodes of acute or chronic rejection and break stable acceptance of allografts in the clinic (67, 74–78). Thus taken together these reports indicate that systemic TLR signals have the capacity to enhance priming and survival of alloreactive T cells, while local tissue-based TLR signals may promote intra-graft recruitment of previously primed alloreactive T cells and enhance the effector phase of the immune response at later time points. The involvement of TLR signals in clinical transplantation is supported by various reports indicating an improved outcome of lung and kidney allografts in patients with TLR4 polymorphisms that result in reduced responsiveness to LPS (79–83).

TLRs IN THE REGULATION OF ALLOGRAFT REJECTION

In addition to augmenting alloimmune responses, sustained TLR engagement may also enhance regulatory loops controlling early inflammatory events post-transplantation and ultimately promote allograft acceptance. Although *in vivo* evidence for TLR-mediated suppression in transplantation is scarce, this view is supported by a number of observations made in infectious or autoimmune settings as discussed below.

Control of innate immune responses

When the immune system and macrophages in particular are exposed to suboptimal concentrations of TLR ligands, they are rendered tolerant to subsequent endotoxin challenge, as characterized by the reduced production of inflammatory cytokines and enhanced secretion of IL-10 and transforming growth factor (TGF)- β (84–86). A similar profile of endotoxin tolerance has been observed in leukocytes from patients with sepsis (85). This desensitization phenomenon and subsequent inhibition of NF- κ B activation can last for several months, as observed after lung infection by influenza or respiratory syncytial virus (87).

Silencing of pro-inflammatory cytokines in LPS-desensitized macrophages correlates with reduced histone acetylation at “tolerizable genes”, such as IL-6, IL-12 and IL-1 β , whereas anti-inflammatory genes such as IL-10 or those coding for antimicrobial effectors remain inducible. (88). In addition to these epigenetic modifications, LPS-desensitized macrophages are characterized by upregulated expression of membrane-bound ST2, a molecule that belongs to the Toll-IL-1R (TIR) superfamily (84, 89). Unlike wild-type mice, ST2-deficient

mice do not develop LPS tolerance and remarkably, administration of soluble ST2-Fc protects wild-type mice from intestinal IRI through an IL-10-dependent mechanism (90). In another study, rats were protected from renal IRI after repeated administrations of low doses of endotoxin which resulted in high intra-renal IL-10 production (91). LPS-desensitization involves other important molecules [reviewed in (89)]. Among them, some behave as either pro-inflammatory mediators or negative regulators, depending on the context. This has been illustrated by the critical role played by the MyD88-independent TRIF/IRF3-dependent pathway of IFN- β production (coupled to TLR4 or TLR3 signaling) in TLR4-mediated endotoxin tolerance (92).

Given the detrimental role of multiple TLRs in IRI or in the prevention of transplantation tolerance, it is interesting to note that desensitization of one TLR (homo-tolerance) can induce tolerance to other TLRs. This so called hetero- or cross-tolerance has been demonstrated for TLR4 ligands and subsequent stimulation through TLRs 2,3 and 9 (92–98). Likewise, chronic stimulation of Nod2, a cytoplasmic NLR (nucleotide-binding domain, leucine-rich-repeat-containing family) protein that binds bacterial peptidoglycan, cross-tolerizes to a subsequent TLR2 or TLR4 stimulation (99). Significantly, a Nod2 polymorphism which is associated with susceptibility to Crohn's disease (100) is also considered an independent risk factor for the development of bronchiolitis obliterans after allogeneic stem cell transplantation (101–103).

Control of adaptive T cell-mediated immune responses

Persistent interactions between microbes and the immune system often result in suppression of T cell responses. TLRs appear to play an important role in this phenomenon which represents one of the mechanisms by which pathogens escape host defenses (104). Moreover, it could explain the protection of individuals infected with parasites from allergic and autoimmune diseases (105–107). The immunosuppression consecutive to repeated exposure to TLR agonists might depend on both direct and indirect effects on T cells. Indeed, TLR2 signaling was shown to be responsible for the enhanced activity of Tregs exposed to HSP60 (108), which might be involved in the regulatory action of HSPs during chronic inflammation (109) and in the preservation of insulin production in diabetic patients treated with a peptide derived from HSP60 (110). However, one should mention that other TLR agonists including TLR4, TLR8 and TLR9 ligands were shown to counteract the suppressive activity of Tregs (26, 111).

In the course of microbial sepsis, suppression of T cell responses was shown to depend on a TLR-mediated expansion of immature GR1⁺ CD11b⁺ myeloid cells (112). Such myeloid-derived suppressor cells have been shown to regulate autoimmune pathologies (113, 114). Their inhibitory function seems to depend on their ability to metabolize L-arginine, leading to L-arginine depletion and the production of nitric oxide, reactive oxygen species and peroxynitrite, inducing T cell apoptosis and prevention of proliferation (115–117). There is suggestive evidence that myeloid suppressor cells are involved in the tolerance to experimental corneal allografts in mice, which depends on programmed death-ligand (PD-L) 1 expression (118).

Finally, the reduced immunogenicity of liver allografts as compared with other organ transplants might involve continuous exposure to TLR agonists since gut-derived bacterial products in portal blood flow were shown to prevent maturation of liver dendritic cells, a phenomenon shown to depend on an IL-6/signal transducer and activator of transcription 3 (STAT3)-dependent pathway (119).

CONCLUDING REMARKS

TLRS expressed on host or recipient cells represent a double-edged sword for solid organ or cell transplants. Whether innate or adaptive immune responses are considered, TLR engagement might indeed be either detrimental or beneficial for allograft outcome (Figure 2). Elucidation of the factors which tip the delicate balance between TLR-mediated events after transplantation could ultimately lead to novel therapeutic strategies based on TLR agonists or antagonists to enhance the outcome of solid organ or cellular allografts.

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Fig 1. TLR2 is overexpressed in human kidney during acute rejection

Immunostaining for TLR2 upon acute cellular rejection (A and B) and in normal kidney (C and D). Few TLR2-positive passenger leukocytes are found in normal renal tissue whereas upon acute rejection TLR2 is visualized on most infiltrating leukocytes as well as in damaged tubules. TLR2 was immunolabeled on frozen sections with light methyl-green staining. Magnification x10 (A and C) and x20 (B and D).

Fig 2. A schematic view of the double-edged sword actions of TLR on the outcome of allografts TLR-related events leading to either rejection or acceptance involve both innate (left) and adaptive (right) arms of the immune response. While mechanisms promoting acute transplant rejection (upper semicircle) have been demonstrated in experimental models, most tolerogenic effects (lower semicircle) are extrapolated from observations made in models of cancer or chronic infection.

Table I

TLR	Leukocytes	references	Parenchymal cells in grafted organs (kidney, liver, heart, skin, lung)	references
TLR1	Ubiquitous		Ubiquitous	
TLR2	Myeloid cells, mast cells, NK cells, Kupffer cells, mDCs, T cells, Treg	(120) (121) (122) (24, 123–125)	Epithelial cells (kidney, liver, lung), endothelial cells (kidney, skin), hepatocytes, hepatic stellate cells, cardiac myocytes, keratinocytes, airway smooth muscle cells	(41) (126) (34, 127–133) (38, 39) (134, 135)
TLR3	mDCs, NK cells, T cells	(23) (120, 124, 136)	Epithelial cells (kidney, liver), mesangial cells (kidney), cardiac myocytes, keratinocytes Airway smooth muscle cells	(41, 127) (38, 137, 138) (39, 134, 135)
TLR4	Monocytes, mast cells, neutrophils, regT cells, T cells, Kupffer cells	(120) (24, 121, 122, 125)	Epithelial cells (kidney, liver, lung), endothelial cells (kidney, liver, skin), hepatocytes, hepatic stellate cells, cardiac myocytes, adventitial fibroblast, keratinocytes, airway smooth muscle cells	(41, 127) (126, 128, 129, 131, 132, 139) (133) (38) (39, 140) (135, 141)
TLR5	NK cells, mDCs, monocytes, neutrophils, T cells, Treg	(23, 24, 120, 122, 124, 125)	Epithelial cells (liver, lung), keratinocytes Airway smooth muscle cells	(126, 127, 142) (134, 135)
TLR6	Myeloid cells, NK cells, mast cells, neutrophils, B cells, Treg	(24, 121, 124, 125, 143)	Epithelial cells (kidney, liver), cardiac myocytes, keratinocytes, airway smooth muscle cells	(41, 127) (38, 39) (135, 144)
TLR7	NK cells, pDCs, neutrophils, eosinophils, B cell, T cells, Treg	(24, 120, 124, 125, 136, 143, 145)	Epithelial cells (liver), cardiac myocytes, airway smooth muscle cells,	(127) (38, 39, 135)
TLR8	NK cells, T cells, B cells, myeloid cells, Treg	(120, 136) (143) (24, 125)	Epithelial cells (liver), cardiac myocytes, airway smooth muscle cells,	(38, 39, 127) (135)
TLR9	pDCs, neutrophils, T cells, B cells, NK cells	(124) (125) (120) (143) (124)	Epithelial cells (liver), keratinocytes, airway smooth muscle cells	(127, 134, 135)
TLR10	Neutrophils, B cells, pDCs	(125) (143) (124)	Epithelial cells (liver), keratinocytes airway smooth muscle cells	(127, 135, 144)
TLR11			Uroepithelial cells, epithelial cells (kidney),	(32)