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Toll-like receptors and damage-associated molecular patterns in the pathogenesis of heart transplant rejection

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Abstract

Significant strides have been made in our understanding of the immune system and its role in cardiac transplant rejection. Despite the growing knowledge of immune responses, the mortality rate following cardiac transplantation remains grim. Related to procedural and pathological complications, toll-like receptor (TLR) and damage-associated molecular pattern (DAMP) signaling is the most direct and earliest interface between tissue integration and the innate immune response. This in turn can activate an adaptive immune response that further damages myocardial tissue. Furthermore, relevant literature on the status of DAMPs in the context of heart-transplantation remains limited, warranting further attention in clinical and translational research. This review aims to critically appraise the perspectives, advances, and challenges on DAMP-mediated innate immune response in the immune-mediated rejection of cardiac transplantation. Detailed analysis of the influence of TLR and DAMP signaling in mounting the immune response against the transplanted heart holds promise for improving outcomes through early detection and prevention of varied forms of organ rejection.

Keywords TLRs · DAMPs · Cardiac transplant rejection · Coronary heart disease · Sterile inflammation

Introduction

About 17.9 million people die from cardiovascular disease (CVD) each year, and in the United States (US), a death from CVD occurs every 36 s on average [1, 2]. Clinically, CVD is an umbrella term for a multitude of diseases of blood vessels, including coronary heart disease (CHD), heart failure, and myocardial infarction (MI). Currently, CVD remains prevalent worldwide. Heidenreich et al. project that about 40% of the US population are at the higher of CVD by 2030 [3]. Interestingly, between 2000 and 2012, the 5-year survival improved from 41 to 48.2% in the United Kingdom; similar to US [4]. Although survival has improved, less than half of patients with newly diagnosed heart disease survive past the 5-year mark.

Heart transplantation (HT) has been considered as a last resort in end-stage HF. Transplant outcomes have been continuously improved by advances in surgical technique and immunosuppressive therapies [5]. Although HT is a life-saving procedure for HF patients, its long-term outcomes remain grim. Immunosuppressive treatment succeeded to increase the 1-year survival rate to greater than 80% and the 5-year survival rate to about 69% [6]. Most long-term complications arise out of infectious diseases, the side effects of immunosuppressive treatments, and progressive cardiac allograft vasculopathy (CAV) in immunocompromised patients [7]. The relevance of the immune response is underlined by these complications and the contemporary advances in transplant survival.

Antibody-mediated rejection (AMR) is the most studied and best described rejection pathway following transplantation. Generally, AMR occurs in approximately 15% of HT recipients, making it the primary cause for cardiac transplant rejection [6]. Symptoms of AMR ranges from mild heart failure to cardiogenic shock [8].

Conventional treatment modalities targeting AMR aim to prevent further immune-mediated injury and provide supportive cardiac treatment, with cardiac re-transplantation reserved for patients who fail in aggressive therapy. Current treatments for AMR consist of plasmapheresis for antibody depletion, immunoadsorption, immunomodulation with intravenous immunoglobulin, and T cell- and B

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cell-depleting drugs; however, most of these lack long-term control of rejection [9, 10]. Considering the post-transplant survival rate, as well as the obvious limitations in targeting the adaptive immune system, it is critical to identify novel translational avenues.

Damage-associated molecular patterns (DAMPs) are the early signals released from injured cells that stimulate immune responses [11, 12]. Numerous studies of solid-organ transplantation have elucidated the potential role of DAMPs as these danger signals activate and regulate the immune response, yet the mechanisms are poorly defined due to the cross-reactivity of pattern recognition receptors (PRRs) with non-self-materials containing pathogen-associated molecular patterns (PAMPs) [13–15] (Table 1). DAMPs are released in perioperative injury during organ procurement and reimplantation and accumulate through organ transplant-specific mechanisms. The accumulation of danger signals is part of the innate immune response which precedes the adaptive immune response and strengthens the signaling mechanisms that constitute transplant rejection. Hence, targeting these mechanisms paves the way to alternate treatment modalities to prevent cardiac allograft rejection. This article critically reviews the advances, perspectives, and challenges of HT with a focus on DAMP-mediated immune response in acute allograft rejection.

Immunosuppressive therapies

Immunosuppressant therapies jumpstarted the modern era of HT in the 1980s leading to the monumental rise in the number of transplant centers and transplanted patients annually [25, 26]. Immunosuppressants have reduced the risk of rejection and minimized the complications. 1-year survival following HT in 1967–1973 was 30%. Between 1982 and 1992, mean survival following HT was increased to 8.5 years due to the introduction of cyclosporine A, a calcineurin inhibitor, which had further increased survival [7, 27]. The median survival rate from 1982 to 2015 was 10.7 years [7]. As of now, immunosuppressive therapies are typically front-loaded immediately after surgery as graft rejection is most common within the first 3–6 months after transplantation [25]. These induction therapies consist of glucocorticoids or glucocorticoid-sparing treatments with agents such as anti-interleukin-2 receptor agonists. The induction dosage is slowly tapered and replaced with long-term maintenance therapy consisting of a triple-drug regimen of prednisone, mycophenolate mofetil, and tacrolimus within hours following surgery [28, 29]. Although this regimen does not improve long-term survival, it reduces the risk of acute rejection [25].

Proliferation signal inhibitors (PSIs) have been used in patients with renal insufficiency, CAV, or malignancies to attenuate or reverse the disease processes [25]. Sirolimus and everolimus are used to inhibit T cell, B cell, and vascular smooth muscle cell proliferation. When used alongside cyclosporine and prednisone, these drugs help prevent acute rejection and slow the progression of CAV in de novo transplant recipients [25, 30]. For patients with chronic CAV, re-transplantation may be an option [30].

Multiple studies have indicated that DAMPs can be targeted therapeutically and that suppressing/inhibiting DAMPs (SAMPs) can be used as candidate drugs [31–35]. SAMPs, such as prostaglandin E2 (PGE2), annexin A1 (AnxA1), and specialized pro-resolving mediators (SPMs) inhibit the proliferation of proinflammatory cytokines, thereby aiding to manage inflammation and prevent further tissue damage instituted by DAMP signaling [36, 37]. These sequential signaling processes must be carefully coordinated and followed by DAMP-promoted tissue repair to avoid the

Table 1 Endogenous damage-associated molecular patterns and their corresponding toll-like receptors

DAMP	Description	TLR	Effect	References
Hsp-60, Hsp-70	Molecular chaperones promoting proper protein folding	2,4	Extracellular HSP contributes to sterile inflammation	[16–19]
HMGB1	Chromatin-associated protein that is passively released from damaged cells or secreted from immune cells		Contributes to increased IL 6 levels post-IRI and stimulates macrophage and neutrophil recruitment	[20]
Fibronectin	ECM component essential for cell communication through binding integrin receptors on the cell surface	4	Increases expression of TNF, worsens systolic function and left ventricular remodeling	[18, 21]
Hyaluronan	Non-sulfated, non-protein glycosaminoglycan important for lubrication			[18, 22]
Heparan sulfate	Acidic, linear polysaccharide with variable structure that is expressed on cell surfaces in the ECM and basement membrane			[18, 23]
Unmethylated CpG DNA	DNA that is not silenced and can be expressed	9	Impairs Treg function and promotes Th1 differentiation	[18, 24]

development of disease [36]. If DAMP and SAMP signaling goes awry, sterile inflammation may become dysregulated. Prolonged DAMP and inadequate SAMP signaling may lead to hyperinflammation or chronic inflammation. On the other hand, immunosuppression from increased SAMP signaling may promote infection [36, 38]. An optimal "DAMP:SAMP ratio" must be achieved for wound healing without additional complications [36]. Land proposes balancing DAMP and SAMP levels to help heal inflammatory diseases, which may be accomplished by administering SAMPs [36, 39]. For now, therapeutic applications in the realm of cardiac transplantation remain unexplored.

Ischemia–reperfusion injury (IRI), a common consequence of transplantation

DAMPs are endogenous molecules that are released during stress, such as IRI, and act upon diverse innate immunity mediating receptors. Tissue injuries in HT relating to the initial state of the donor organ, preservation conditions, and potential ischemia–reperfusion injury (IRI) cause the release of various DAMPs [40]. The interaction between DAMPs and toll-like receptors (TLR) induces the release of pro-inflammatory cytokines, leading to the recruitment of neutrophils and macrophages at the site of injury to trigger an immune cascade [40, 41]. Sterile inflammation, or inflammation in the absence of a pathogen, contributes to DAMP release and subsequent allograft injury [13, 42, 43].

In IRI, ischemia during organ procurement results in cellular hypoxia and reduced ATP production. The lack of ATP disrupts the Na^+–K^+ ATPase pump and subsequently results in an influx of Na^+ and water leading to cell swelling, dysregulated Ca^{2+}, release, and disruption of cell membrane proteins [42]. Receptors in graft endothelial cells respond to the lack of blood flow in IRI by depolarizing the endothelial cell membrane, activation of NADPH oxidase, and production of reactive oxygen species (ROS) [44–47]. Reperfusion leads to the formation of superoxide radicals causing lipid peroxidation and the secretion of pro-inflammatory cytokines including CXCL1, CXCL2, TNF-α, IL-8, and IL-17 [48, 49]. The barrage of inflammatory cytokines worsens the inflammation already caused by ischemia.

Following IRI in the heart, there is intramyocardial deposition of iron [42]. Any residual myocardial iron contributes to ferroptosis causing adverse cardiac remodeling post-reperfusion [42, 50, 51]. This process results in DAMP release and contributes to neutrophil adhesion to coronary vascular endothelial cells via the TLR4-Trif-Type I IFN-dependent signaling axis [42, 52, 53]. Li et al. have shown that treatment with ferrostatin-1, as well as coronary artery ligation, inhibited ferroptosis, improving systolic function and ventricular remodeling [42, 52]. Preventing ferroptosis will also

reduce DAMP release that leads to further myocardial damage (Fig. 1).

DAMPs in transplant rejection

DAMPs released from myocardial injuries, such as post-transplant IRI, lead to transplant rejection. Studies discovered histones, heat-shock proteins (HSPs), high-mobility group box 1 (HMGB1), DNA, rRNA, miRNA, and ATP as possible danger signals in transplantation aggravating the inflammation [40, 54]. HMGB1 is the most studied DAMP involved in transplant rejection. Following transplantation, HMGB1 is significantly upregulated [55]. HMGB1 is passively secreted from cells damaged in organ harvest and IRI and actively released by immune cells within the allograft. By interacting with DNA released by necrotic cells, HMGB1 upregulates pro-inflammatory pathways through PRRs such as TLR2, and TLR4 and induces macrophages-driven IL-23 [42, 45, 56, 57]. IL-23 stimulates γδ T cells to release IL-17A, which results in cardiomyocyte apoptosis and neutrophil recruitment [57]. Treatment with rA-box, an endogenous HMGB1 inhibitor, has been shown to delay heart allograft rejection by 1 week and reduced levels of proinflammatory cytokines including TNF-α [55]. Furthermore, inhibition of the HMGB1-IL-23/IL-17 pathway via glycyrrhizin or necrostatin-1 alleviates myocardial IRI suggesting the potential role of HMGB1 in IRI [42, 45, 58]. Necrostatin-1 is a non-specific necroptosis inhibitor that also inhibits ferroptosis [42]. HMGB1's regulation of a variety of processes that culminate in IRI and graft rejection makes it an excellent therapeutic target to reduce potential myocardial damage.

ATP is the primary energy source used in most cellular functions. Small amounts of ATP exist extracellularly (eATP). The release of ATP from apoptotic or damaged endothelial cells and platelets after IRI disrupt the cell's ability to carry out homeostasis [42]. eATP acts as a DAMP that binds to P2X7R and results in Nod-like receptor protein 3 (NLRP3) inflammasome activation and release of IL-1β during injury [42, 59]. Furthermore, eATP acts as a mitogen to induce cell cycle proliferation and tyrosine phosphorylation [11]. Vergani et al. evaluated the expression of P2X7R in cardiac transplants in murine models and noted its significant upregulation [60]. Next, short-term inhibition of P2X7R with periodate-oxidized ATP increased graft survival to greater than 100 days in 80% of murine transplant recipients [60, 61] (Table 2). Additionally, Vergani et al. noted the reduction of CD4+ T cells, CD8+ T cells, regulatory T cells, and Th17 [60]. Overall, the study has shown that the ATP/P2X7R pathway is another potential target that can improve cardiac transplant rejection and long-term graft survival [59, 60].
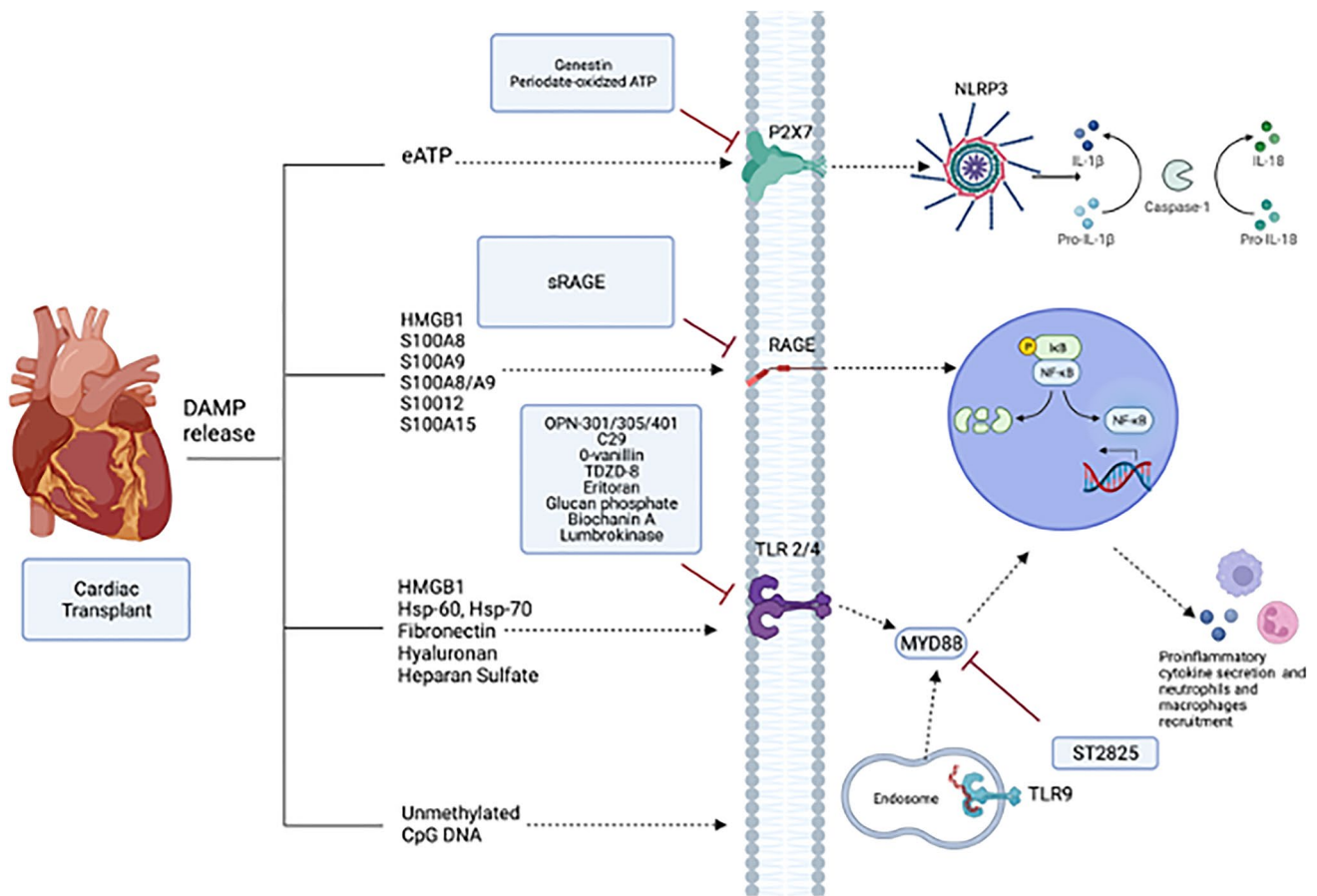
Fig. 1 IRI during cardiac transplantation results in DAMP release. Coordinated DAMP signaling cascades promote inflammation via activation of mediators. DAMPs, receptors, and mediators can be inactivated or blocked by experimental therapeutics

Table 2 Experimental therapeutics targeting DAMP signaling in myocardial IRI

Receptor target	Experimental therapeutic	Effects	References
Fibronectin-EDA	Anti-fibronectin-EDA antibody	Reduction of myocardial infarct (MI) size	[62, 63]
mtDNA	Epigallocatechin-3-gallate	Reduction of MI size and severity of myocardial injury; decreased incidence of ventricular arrhythmia	[62, 64]
exRNA	Rnase	Reduction of myocardial cytokine response, caspase-3 activation, and MI size	[62, 65]
	Dex-TO	Reduction in macrophage infiltration and MI size	[62, 66]
	SiRNA (NONRATT021971)	Increase in cervical superior sympathetic activity	[62, 67]
P2X7	Genestin	Antioxidant and anti-inflammatory effects	[62, 68]
	Periodate-oxidized ATP	Anti-inflammatory effects; improved graft survival	[60, 62]
Hyaluronan (HA)	4-MU	Inhibition of HA synthesis	[69]

The S100 protein family is produced by cells of myeloid origin and has been linked to CAV. Several members of the family, such as S100A8, S100A9, S100A8/A9, S100A12, and S100A15, function as DAMPs that trigger endothelial cells and other cell types to produce inflammatory cytokines and chemokines [70]. Myeloid cell activation and tubulin-dependent translocation to the plasma membrane mediates S100 protein release [56]. Subsequently, S100 proteins lead to inflammation by binding to a variety of cell surface receptors such as RAGE and TLR4. Studies examining lung allograft stability have found the elevation of S100 proteins in patients with restrictive allograft syndrome compared to control patients with stable graft function [70]. In contrast, expression of

S100A8 in kidney allografts was associated with a reduced incidence of CAV. Inhibition of RAGE with murine soluble RAGE (sRAGE) has been attributed to improvement of graft survival and a reduction in S100 [62, 71, 72]. Although the role of S100A8/9 in HT has not been elucidated, it is potentially involved in atherogenesis, ischemia-associated MI, and heart failure [62, 70]. Due to its role in enhancing inflammation, S100A8/9 potentially plays a role in heart transplant rejection (HTR); however, warrants further research [73].

Extracellular matrix molecules act as DAMPs in the setting of HTR. Molecules, such as heparan sulfate proteoglycan (HSPG) and fibronectin, enhance and modulate the pro-inflammatory state [54, 74]. HSPG is an acidic linear polysaccharide in the extracellular matrix and basement membrane of mammalian cells. HSPG and soluble heparan sulfate are heavily involved in tissue repair mechanisms and clearance of cellular debris. As DAMPs, these molecules interact with TLR4 to release proinflammatory cytokines and promote the maturation of dendritic cells [74, 75]. Fibronectin performs various functions, such as cell differentiation, proliferation, and extracellular matrix assembly [76]. When fibronectin functions as a DAMP, it recruits lymphocytes and helps induce their migration to the site of injury [77]. Chorawala et al. confirmed the importance of fibronectin as a proinflammatory signaling molecule using a mouse-model where 15 min post-transfusion anti-fibronectin antibodies significantly reduced IRI [63].

Hyaluronan, also known as hyaluronic acid (HA), is a ubiquitous extracellular matrix (ECM) glycosaminoglycan and acts as another DAMP that is released during injury and infection [14, 42]. HA degrades to high-weight (HMW-HA) and low-weight molecular forms (LMW-HA) [42, 45, 78]. The LMW-HA dominates in triggering pro-inflammatory events via TLR4 signaling to stimulate the maturation of monocyte-derived dendritic cells and upregulate TNF-α, IL-1β, and IL-12 [42]. Hällgren et al. visualized HA in rat heart grafts at various time points after transplantation. In normal, non-transplanted hearts, HA was seen in myocardial interstitial tissue and in the adventitia of arteries and veins [79]. By day 6 post-transplantation, cardiac allografts displayed threefold increase in HA levels in areas with edematous interstitial tissue due to leukocyte infiltration. Hackert et al. demonstrated the role of hyaluronan using 4-methyl-umbelliferone (4-MU), a naturally occurring coumarin that inhibits hyaluronan synthesis and deposition [69]. They observed that 4-MU reduces cardiac remodeling, perivascular and interstitial left ventricular fibrosis, and cardiomyocyte fibrosis. Although some studies have reported proinflammatory properties of HA, there are conflicting reports discussing its anti-inflammatory effects warranting further investigations [14, 78, 80, 81].

Cardiac transplant pathology and toll-like receptors

Studies have predominantly focused on the role of the adaptive immune response in AMR, though recently, investigations found a critical role of DAMP and TLR regulation activity in mediating the adaptive immune response in AMR [74]. Following the discovery of TLRs, the innate immune system has been at the forefront of immunological research [74, 82]. These receptors are expressed in a multitude of hematopoietic cells, endothelial cells and organ parenchymal cells [40, 41, 83]. Unlike T cell receptors and antibodies, TLRs lack a vast reserve of antigen recognition epitopes; however, they excel in immediate recognition of ligands and eliciting the downstream response.

Canonically, TLRs have been associated with antimicrobial defense against foreign pathogenic particles, such as lipopolysaccharide (LPS) or viral DNA and RNA. The most studied TLRs include TLR2 and TLR4. TLR2 forms heterodimers with TLR1 or TLR6 upon recognition of peptidoglycan on Gram-positive bacteria and bacterial lipoproteins [84]. TLR4 forms heterodimers with MD2 and CD14 upon recognition of LPS on Gram-negative bacteria. The function of TLRs has recently expanded to include interactions with DAMPs such as HMGB1 [85]. Studies of TLR4- and TLR2-deficient mice have found increased survival rates post-IRI compared to WT mice [42]. Although leukocyte infiltration was similar between deficient and WT groups, TLR2-deficient mice exhibited minimal myocardial damage in non-infarcted regions of the heart suggesting the regulatory roles of TLR2 and TLR4 in post-IRI myocardial damage and remodeling. Many similar studies have also identified potential therapeutics that target TLR2 and TLR4 signaling, thus attenuating myocardial damage from IRI (Table 3).

In transplantation, alloimmunity has been achieved by the knockout of MyD88, the universal TLR signal adapter protein [84]. By disarming MyD88 pro-inflammatory signaling pathways, such as those involving IL-1 and IL-18, Goldstein et al. demonstrated that TLRs are activated by molecules other than traditional PAMPs. Additionally, halting IL-18 signaling by MyD88 knockout could halt processes that mediate rejection, such as IRI [94]. Their study found that MyD88 knockout mice survived more than 100 days following skin transplant whereas wild-type mice rejected the allograft and survived a median of 16 days [84]. In addition, He et al. demonstrated similar results where a short course of MyD88 inhibitor, ST2825, significantly prolonged post-transplant survival of mouse cardiac allografts [95]. Moreover, the ST2825 treatment reduced necrosis and graft infiltration with inflammatory

Table 3 Experimental therapeutics targeting TLR signaling in myocardial IRI

Receptor target	Experimental therapeutic	Mechanism of action	References
TLR2	OPN-301	Inhibition of TLR2-mediated pro-inflammatory cytokine production	[86]
TLR2	OPN-305	Inhibition of TLR2-mediated pro-inflammatory cytokine production	[87]
TLR2	C29	Inhibition of TLR2 with MyD88 and blockade of NF-kB activation	[88]
TLR2	o-Vanillin	Inhibition of TLR2 signaling	[88]
TLR2	TDZD-8	Inhibition of TLR2 transcription	[89]
TLR4	OPN-401	Inhibition of TLR4-dependent signaling	[87]
TLR4	Eritoran	Antagonism of NF-kB translocation	[90]
TLR4	Glucan phosphate	Inhibition of TLR4 association with MyD88 to prevent NF-kB activation	[91]
TL4 and NLRP3 inflammasome	Biochanin A	Inhibition of TLR4/NF-kB signaling and NLRP3 inflammasome suppression	[92]
TLR4	Lumbrokinase	Inhibition of TLR4 signaling	[93]

cytokines. Furthermore, Hsieh et al.'s mouse-model study on bone allograft rejection has described the upregulation of MyD88 and TLR-4 in femoral allografts [96]. Since the MyD88-TLR4 signaling pathway is upregulated in femoral allograft rejection, it may potentially be involved in the pathogenesis of cardiac transplant rejection. A seminal study by Frye et al. demonstrated that CCR2+ macrophages produce CXCL5 in a TLR9/MyD88-dependent fashion, promoting and regulating the extravasation of neutrophils [42, 97]. The upstream extravasation is mediated through TLR-4/Trif/type I IFN signaling pathways in endothelial cells that are activated through ferroptotic cell death of graft cells. Additionally, Li et al. have shown that neutrophil extravasation into inflamed myocardial tissue is also mediated via TLR9/MyD88/CXCL5 signaling [97]. Specifically, TLR9 regulates the expression of neutrophil chemoattractants, thereby contributing to the neutrophil trafficking responsible for IRI. MyD88 deficient macrophages can adequately inhibit neutrophil extravasation, preventing further damage to an already injured heart.

TLR downstream signaling effects include inflammasome assembly [42]. The inflammasome is a macromolecular, intracellular complex responsible for amplifying inflammatory signals and can be activated by TLR2, TLR3, TLR4, TNFR1, or IL-1R stimulation [42, 98]. Once priming of the inflammasome complex occurs through post translational modification of NLRP3 or Nuclear Factor-kB (NF-kB) augmentation of inflammasome components (NLRP3, caspase-1, and ASC) and cytokines (pro-IL-1b and pro-IL-18), the inflammasome produces caspase-1. Caspase-1 results in the production of IL-1b and IL-18, leading to inflammation [99]. Shah et al. performed biopsies of human hearts following cardiac transplant rejection which revealed inflammasome "specks" in 7 of 8 hearts [42, 98]. The presence of these "specks" indicates that inflammasome activation potentially has a role in cardiac transplant rejection.

DAMP binding to PRRs and TLRs activates the adaptive immune system through costimulatory molecules and cytokine stimulation of macrophages. Macrophages reprogrammed through epigenetic changes and metabolic signaling to develop immunologic memory and hypersensitivity to stimulation [42, 100]. Local modulation of macrophages through PRRs, dectin-1 and TLR4 has been shown to amplify this reprogramming, leading to transplant rejection. Dectin-1 has been localized to apoptotic tissues in rejection [42]. This is significant since apoptotic tissues in donor organs upregulate the production of vimentin, an endogenous molecule involved in wound healing which is a potent ligand for dectin-1 [42, 100, 101]. In addition, HMGB1 signaling contributes to the reprogramming of immunity leading to the release of proinflammatory cytokines [42].

Conclusion and future directions

Rejection is a major complication following solid-organ transplant. Review of current literature on the role of the innate immune system in cardiac allograft rejection indicates the potency of DAMPs and their corresponding TLRs in the initial alloimmune response associated with HTR. DAMPs play a significant role in the initial stages of solid-organ transplant rejection by eliciting a rapid immune response. Currently, most studies explore the role of DAMPs in kidney and lung transplantation. Although DAMP pathways in cardiac transplant rejection remain unexplored, their implications in IRI and other transplanted organ rejections suggest that the transplanted heart most likely responds in a similar manner.

Considering the lack of therapies targeting the innate immune system, a better understanding of DAMP signaling pathways in HT failure may support potential interventions in the future transplantation medicine. Therapeutics that block the initial DAMP release may prevent or delay

further complications along the signaling pathway. Furthermore, blocking DAMP-TLR interactions possibly prevent the downstream inflammatory effects of this interaction. Investigation on DAMPs, and their corresponding TLRs, would open beneficial therapeutic regimes to patients who are resistant to the current available options. Drugs that possibly target DAMP binding and signal transduction could prevent the devastating effects of acute allograft rejection. Encouragingly, emerging research in the involvement of DAMPs in HTR could open several translational avenues in the management of transplant failure.

Data availability Not applicable; all information is gathered from published articles.

Code availability Not applicable.

Declarations

Conflict of interest The authors declare no conflict of interest.

Ethical approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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