Review Article

The role of CD38 in ischemia reperfusion injury in cardiopulmonary bypass and thoracic transplantation: a narrative review

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Background and Objective: Ischemia reperfusion injury (IRI) is often the underlying cause of endothelium breakdown and damage in cardiac or transplantation operations, which can lead to disastrous post-operative consequences. Recent studies of cluster of differentiation 38 (CD38) have identified its critical role in IRI. Our objective is to provide a comprehensive overview of CD38-mediated axis, pathways, and potential CD38 translational therapies for reducing inflammation associated with cardiopulmonary bypass (CPB) or thoracic transplantation and IRI.

Methods: We conducted a review of the literature by performing a search of the PubMed database on 2 April 2023. To find relevant publications on CD38, we utilized the MeSH terms: "CD38" AND "Ischemia" OR "CD38" AND "Transplant" OR "CD38" AND "Heart" from 1990–2023. Additional papers were included if they were felt to be relevant but were not captured in the MeSH terms. We found 160 papers that met this criterion, and following screening, exclusion and consensus a total of 36 papers were included.

Key Content and Findings: CD38 is most notably a nicotine adenine dinucleotide $(NAD)^+$ glycohydrolase (NADase), and a generator of Ca^{2+} signaling secondary messengers. Ultimately, the release of these secondary messengers leads to the activation of important mediators of cellular death. In the heart and during thoracic transplantation, this pathway is intimately involved in a wide variety of injuries; namely the endothelium. In the heart, activation generally results in vasoconstriction, poor myocardial perfusion, and ultimately poor cardiac function. CD38 activation also prevents the accumulation of atherosclerotic disease. During transplantation, intracellular activation leads to infiltration of recipient innate immune cells, tissue edema, and ultimately primary graft dysfunction (PGD). Specifically, in heart transplantation, extracellular activation could be protective and improve allograft survival.

Conclusions: The knowledge gap in understanding the molecular basis of IRI has prevented further development of novel therapies and treatments. The possible interaction of CD38 with CD39 in the endothelium, and the modulation of the CD38 axis may be a pathway to improve cardiovascular outcomes, heart and lung donor organ quality, and overall longevity.

Keywords: Cluster of differentiation 38 (CD38); ischemia reperfusion injury (IRI); cardiopulmonary bypass (CPB); thoracic transplantation

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Introduction

Cardiothoracic surgeons specialize in supporting the body through cardiopulmonary bypass (CPB) and mechanical circulatory support in order to perform a variety of life-saving operations. This includes stopping and starting blood flow to the heart during CPB, and to the donor heart or lungs during procurement and subsequent organ transplant. The ischemia caused by the lack of blood flow, as well as the reestablishment of blood flow, results in an injury known as ischemia reperfusion injury (IRI). IRI ultimately results in dysregulation of cellular homeostasis, the breakdown of the endothelial barrier and ultimately cell death (1-3). Although this injury can affect all organs, some of the most devastating consequences arise from IRI in the heart and lungs (4,5).

Although many molecular pathways lead to endothelial cellular injury, a common pathway leading to injury revolves around cluster of differentiation 38 (CD38). CD38 is an evolutionarily conserved multifunctional enzyme found in a wide variety of tissues and was originally discovered as an antigen marker on lymphocytes (6). It was later found to have adenosine diphosphate (ADP) ribosyl cyclase, cyclic ADP ribose (cADPR) hydrolase, nicotine adenine dinucleotide (NAD)$^+$ glycohydrolase (NADase) and nicotinamide adenine dinucleotide phosphate (NADP)$^+$ phosphatase (NADPase) function (*Figure 1*) (3). Today its primary and most widely recognized function is to serve as a major NADase in the body, which generates crucial secondary messengers for calcium mobilization: cADPR and nicotinic acid adenine dinucleotide phosphate (NAADP) (7,8). cADPR and NAADP are involved in the mobilization and equilibration of intracellular calcium, a prerequisite for maintaining cellular function, metabolism, and signaling (7). The NAD$^+$/CD38/cADPR/Ca^{2+} axis is intimately involved in the production of inflammatory cytokines and signals, and indirectly regulates cell survival (2,3,9-12).

CD38 exists in two main typologies: type II, which is mainly extracellularly bound on the plasma membrane or inside endosomes or vacuoles, or type III, which is within the cytosol on the membrane of organelles such as the endoplasmic reticulum. This creates a typological paradox as CD38's substrates (NAD$^+$/NADP$^+$) and its products (cADPR/NAADP) are located intracellularly (13-16). This notion is important to understand when determining which CD38 typology is activated, as this can lead to an increase or decrease in the inflammatory response and thus cell survival and longevity (5,17,18). By intervening on the fundamental molecular mechanisms that affect IRI, rather than mitigating its side-effects, CD38 modulation is a promising novel therapeutic target during CBP or thoracic transplantation.

The objective of this narrative review is to provide: (I) a basic overview of the NAD$^+$/CD38/cADPR/Ca^{2+} axis; (II) the current understandings of the role of CD38 in IRI as it relates to CPB and transplantation; (III) CD38 modulation, and future directions of novel therapies to improve IRI-related injury and; (IV) explore the potential interaction of CD38 with CD39 in cardiovascular stress. We present this article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-23-725/rc) (19).

Methods

We conducted a review of the literature by performing a search of the PubMed database on 2 April 2023. To find relevant publications on CD38 we utilized the MeSH terms: "CD38" AND "Ischemia" OR "CD38" AND "Transplant" OR "CD38" AND "Heart" from 1990–2023. We included all papers that discussed CD38 in the context of IRI, thoracic transplantation, cardiac surgery, cardiac related IRI or could provide underlying mechanisms of CD38 that would provide historical or mechanistic background to the reader. Exclusion criteria included papers that discussed CD38 in the context of non-relatable disease states or treatments (i.e., cancer, bone marrow transplant, kidney or liver disease) and pathophysiology not related to IRI. Additionally, due to the novelty of this topic, papers were included that were referenced in papers from the original PubMed search (but for reasons unknown did not yield a search result PubMed) if they met the inclusion criteria. Using this search method, a total of 146 articles were found, and after inclusion and exclusion, and final selection 36 papers were included (Figure S1). The selection process was conducted amongst the authors: Gouchoe DA, Vijayakumar A, Aly AH and Cui EY. Consensus was obtained

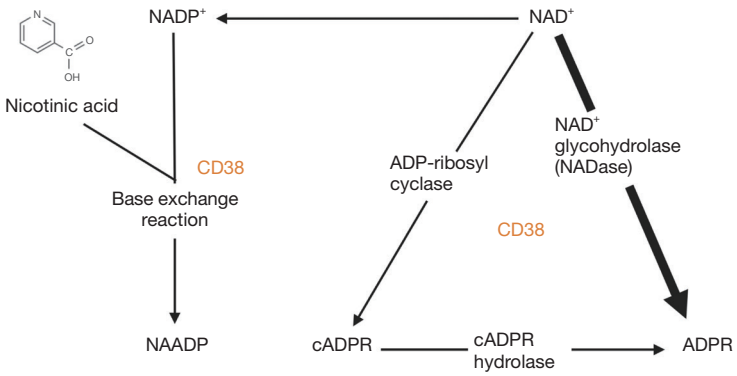

Figure 1 The NAD^+/CD38/cADPR/Ca^{2+} axis. NAD^+ is converted to cADPR by ADP-ribosyl cyclase and to ADPR by NAD^+ glycohydrolase; additionally, ADPR can be generated by cADPR hydrolase. NAD^+ turns into $NADP^+$ and subsequently NAADP by base exchanges facilitated by CD38. NAD, nicotine adenine dinucleotide; ADP, adenosine diphosphate; cADPR, cyclic ADP ribose; ADPR, ADP ribose; NADP, nicotinamide adenine dinucleotide phosphate; CD38, cluster of differentiation 38; NAADP, nicotinic acid adenine dinucleotide phosphate.

Table 1 Search strategy

Items	Specification
Date of search	4/2/2023
Databases and other sources searched	PubMed
Search terms used	"CD38" AND "Ischemia" OR "CD38" AND "Transplant" OR "CD38" AND "Heart"
Timeframe	1990–2023
Inclusion and exclusion criteria	Inclusion: papers that discussed CD38 in the context of IRI, thoracic transplantation, cardiac surgery, cardiac related IRI or could provide underlying mechanisms of CD38 that would provide historical or mechanistic background to the reader
	Exclusion: papers that discussed CD38 in the context of non-relatable disease states or treatments (i.e., cancer, bone marrow transplant, kidney or liver disease) and pathophysiology not related to IRI
Selection process	The selection process was conducted amongst the authors: Gouchoe DA, Vijayakumar A, Aly AH and Cui EY. Consensus was obtained if a majority felt that it should be included or if the paper was needed to provide adequate background information to the reader
Any additional considerations	Additionally, due to the novelty of this topic, papers were included that were referenced in papers from the original PubMed search (but for reasons unknown did not result in PubMed) if they met the inclusion criteria

CD38, cluster of differentiation 38; IRI, ischemia reperfusion injury.

if a majority felt that it should be included or if the paper was needed to provide adequate background information to the reader. Full details on the search strategy can be seen in *Table 1*.

NAD^+/CD38/cADPR/Ca^{2+} axis

A critical event and sequelae in IRI is the breakdown of the endothelial barrier due to the underlying injury or insult. The NAD^+/CD38/cADPR/Ca^{2+} axis is a common pathway leading to injury and endothelial barrier dysfunction (2,3). When cells are injured, there is an activation of CD38 and resulting consumption of NAD^+ and $NADP^+$, and the production of secondary messengers: cADPR and NAADP (2,3).

NAD^+ is a crucial coenzyme, serving a significant role in oxidation-reduction reactions and participating in the regulation of inflammatory and metabolic homeostasis

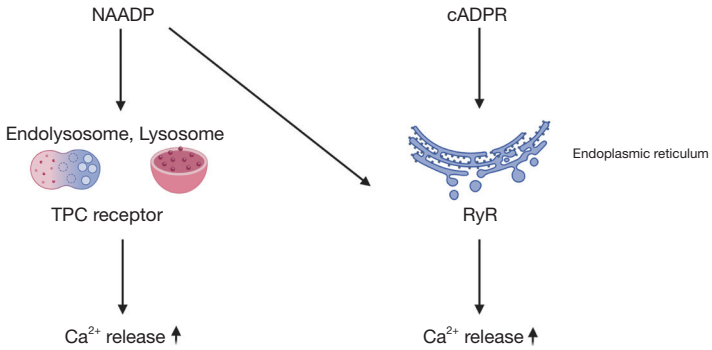

Figure 2 CD38 activity results in the production of potent Ca^{2+} mobilizing secondary messengers: cADPR and NAADP. cADPR regulates intracellular Ca^{2+} homeostasis by functioning as the signal for Ca^{2+} release via ryanodine receptor activation. NAADP maintains intracellular Ca^{2+} homeostasis by signaling Ca^{2+} release from the two-pore channel receptor located in lysosomes, endolysosomes, or from ryanodine receptor as well. NAADP, nicotinic acid adenine dinucleotide phosphate; TPC, 2-pore channel; cADPR, cyclic ADP ribose; ADP, adenosine diphosphate; RyR, ryanodine receptor; CD38, cluster of differentiation 38.

(10,20). $NADP^+$ is another essential coenzyme involved in mitochondrial and metabolic pathways, and its dysregulation causes increased oxidative stress (5). Furthermore, consumption of NAD^+/$NADP^+$ prevents these cofactors from being available to other NAD^+-dependent deacetylases, which are important in cell signaling and cell metabolism (10). The generation of cADPR and NAADP causes a surge in intracellular Ca^{2+} (*Figure 2*). cADPR regulates intracellular Ca^{2+} homeostasis by acting as the signal for Ca^{2+} release via ryanodine receptor activation (21,22), while NAADP maintains intracellular Ca^{2+} homeostasis by signaling Ca^{2+} release from the two-pore channel receptor located in lysosomes, endolysosomes, or the ryanodine receptor (18-20). Because it controls many cellular functions, dysregulation of Ca^{2+} results in the elaboration of inflammatory cytokines, reactive oxygen species (ROS), and overall skewing of the cell towards an inflammatory phenotype (23,24). Therefore, the NAD^+/CD38/cADPR/Ca^{2+} axis can directly regulate inflammation and indirectly regulate cell survival.

The CD38 typological paradox

The CD38 exists in two main typologies, i.e., the orientation of a molecule in 3D space: type II and type III. CD38 has traditionally been characterized as a glycosylated cell surface protein (type II) protein with an extracellular catalytic domain (25). Type II CD38 functions to maintain NAD^+ turnover in the extracellular environment, as well as regulate precursors of its synthesis (26). As has been described, this creates a typological paradox. The substrates (Ca^{2+}, NAD^+ and $NADP^+$) and their products (cADPR, NAADP) are located primarily in the cytosol and (13,27), while the site of primary CD38 action was thought to be extracellular. However, a recent study has identified that CD38 also exists in a non-glycosylated type III typology (*Figure 3*) with the catalytic domain oriented to the cytoplasm (27). Type III CD38 is present on the membranes of cytosolic organelles including the nucleus, mitochondria, endoplasmic reticulum, and lysosomes; where it can regulate its substrates (Ca^{2+}, NAD^+ and $NADP^+$) (13-16). This principle is important to understand when determining which typology of CD38 is activated, as this can lead to an increase or decrease cytokine production, as well as a protective or harmful result for the cell (5,17,18).

CD38's role in programmed cellular death

IRI is a complex process mediated by many damage-associated molecular patterns (DAMPs) and inflammatory signaling cascades that lead to impaired cell function, ultimately leading to endothelial cell death (28). One such factor is nuclear factor-Kβ (NF-Kβ) (29), which translocates to the nucleus and increases the transcription levels of pro-interleukin (IL)-1β, pro-IL-18 and NOD-like receptor protein-3 (NLRP3) (30,31). Additionally, NF-Kβ serves as a transcription factor for CD38, promoting its production (32,33). As discussed previously, CD38 activation increases intracellular Ca^{2+} and ROS production (23,24). This is important as both Ca^{2+} and ROS are the activators of

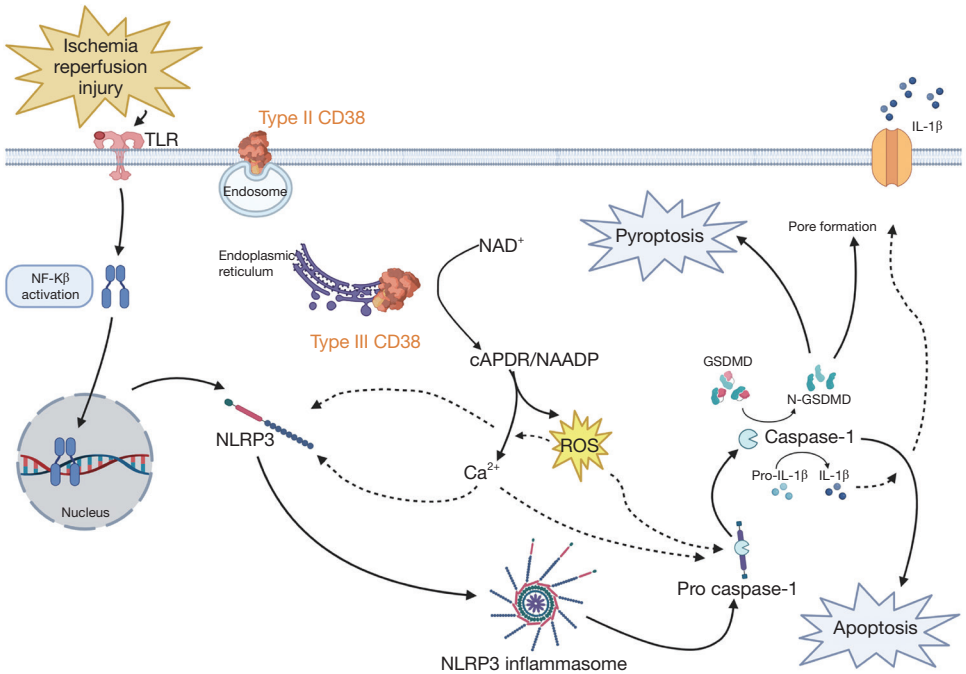

Figure 3 CD38 inflammatory cascade. IRI activates NF-Kβ and CD38; NF-Kβ translocates to the nucleus and increases the transcription levels of pro-IL-1β, pro-IL-18 and NLRP3. Activation of CD38 leads to a rise in intracellular Ca^{2+} and ROS production, which activates NLRP3 to allow the formation of the NLRP3-inflammasome. The NLRP3-inflammasome turns pro-caspase-1 into its active form, caspase-1, which leads to apoptosis and pyroptosis. TLR, Toll-like receptor; CD38, cluster of differentiation 38; IL, interleukin; NF, nuclear factor; NLRP3, NOD-like receptor protein-3; NAD, nicotine adenine dinucleotide; cADPR, cyclic ADP ribose; ADP, adenosine diphosphate; NAADP, nicotinic acid adenine dinucleotide phosphate; ROS, reactive oxygen species; N-GSDMD, N-gasdermin-D; IRI, ischemia reperfusion injury.

NLRP3, which allows the formation of the NLRP3-inflammasome (34-38). Once this is complete, the NLRP3-inflammasome cleaves pro-caspase-1 into its active form, caspase-1.

Caspase-1 has a diverse set of functions, but most importantly can trigger two kinds of programmed cell death: apoptosis and pyroptosis. Apoptosis is a form of programmed cell death characterized by a controlled dismantling of cellular architecture that leads to cell death and prepares cells for removal by phagocytes without triggering an unwanted immune response. Cells induce death through proteolysis ultimately from caspase-3/6/7 (39,40). Several studies have highlighted that caspase-1 activates caspase-3, although exact mechanisms are yet to be elucidated (41-44). Furthermore, caspase-1 activates caspase-8, which serves as the activator of caspase-3/6/7 (40,42,45,46). Pyroptosis is another form of programmed cell death and is more often associated with IRI than apoptosis (47). It differs from apoptosis in that cell death arises from plasma membrane disruption, organelle swelling, and mitochondria dysfunction. Caspase-1 most commonly is associated with cleaving gasdermin-D (GSDMD) into N-GSDMD, pro-IL-1β to IL-1β and pro-IL-18 to IL-18 and subsequently initiates pyroptosis. During pyroptosis, N-GSDMD interacts with the cell membrane to form transmembrane pores which allows IL-1β, IL-18 and additional signals to be released promoting further inflammation and cell death (40,47). A summary of this cascade can be seen in *Figure 3*.

Clinical applications of CD38 mediated IRI and modulation

Reducing CPB associated IRI

Inherent to cardiac surgery and CPB, is the cessation and resumption of blow flood. Additionally, the blood-bypass circuit interaction activates inflammatory cascades. This pause and resumption of blood flow causes IRI in heart tissue

during any cardiac operation that requires arresting the heart. IRI in the heart begins with oxidative stress, inflammation, and intracellular calcium overload and rapidly progresses to irreversible cell death by apoptosis and pyroptosis (48-51). IRI was first described in the heart by Jennings *et al.* when canine hearts underwent temporary coronary occlusion, resulting in visible histological changes (52). Clinically, after arresting the heart during CPB, IRI can result in arrhythmia, myocardial stunning, low cardiac output syndrome, and perioperative myocardial infarction (53).

In patients with perioperative mortality soon after coronary artery bypass surgery, histological evidence of IRI can be seen in 25–45% of patients (54,55). One potential significant contributor to the CPB associated inflammatory response is the IRI associated with cessation of ventilation and the associated development of atelectasis during CPB. Apnea, atelectasis, and hyperoxia during CPB create a pro-inflammatory state and foster IRI, and invariably increase pulmonary vascular resistance, impair right ventricular performance, and cause low cardiac output syndrome (56-58). Although few studies, such as the MECANO trial, have indicated a potential benefit to continued ventilation during CPB, the ideal ventilatory strategy and the fraction of inspired oxygen remain to be determined (59,60). Besides the PROVECS trial, which reported lung damage from alveolar distention is associated with an increase in soluble receptor advanced glycation end-products (sRAGE), other markers of molecular injury have not been studied in depth (61,62). In order to further study the role of ventilatory strategy, inflammation, and outcomes on CPB and the interaction of CD38 at large—the FOCUS trial is being used to look at this relationship specifically at select centers. The large, randomized, prospective, multicenter FOCUS trial (NCT04978636, "*The eFfect of cOntinuous Low Tidal Volume Ventilation With Hyperoxia Avoidance During CardiopUlmonary Bypass*"). The primary objective of the study is to investigate the effect of continuous low-tidal volume ventilation with hyperoxia avoidance (using FiO_2 of 0.21) during CPB on postoperative pulmonary complications (PPCs) and 30-day mortality. Secondly, the FOCUS trial will determine the effects of these ventilatory approaches on lung injury and serum markers of IRI [sRAGE (63) and 8-isoprostaglandin F2α (64)], in addition to tracking levels of CD38 to determine the activity levels and its association with PPCs. The main hypothesis is that PPCs and mortality will be reduced in cardiac surgical patients receiving low-tidal volume ventilation with FiO_2 =0.21 during CPB, and that serum markers of inflammation, such as CD38, will be reduced.

IRI has been shown to upregulate CD38 activity in the heart when exposed to injury (3). Subsequently, this increased activity leads to the depletion of NAD^+/$NADP^+$. At the endothelial level, the reduction of NAD^+/$NADP^+$ limits the function of oxidoreductase endothelial nitric oxide synthase (eNOS), increases the production of ROS and overall leads to poor cell function (5,65,66). Globally, impaired eNOS function limits nitric oxide (NO) production leading to vasoconstriction, poor myocardial perfusion, and ultimately decreased cardiac activity (3,67). In addition, upregulation leads to an increase in intracellular calcium. Dysregulation of calcium homeostasis within the cytoplasm results in delayed after depolarizations and ultimately arrhythmias for the patient (68-70). Finally, the consumption of NAD^+ by CD38 impacts many other NAD^+ dependent pathways. Decreasing levels of NAD^+ leads to diminished activity of sirtuins, which are important mediators of antioxidants and inactivity leads to an increase in oxygen stress on cardiomyocytes (71,72). Thus, CD38 plays a vital role in facilitating cardiac dysregulation, damage, and arrhythmias and ultimately contributes to poor function and outcomes for patients suffering from IRI after CBP.

Several studies have examined CD38 genetic ablation and its effect on IRI in hearts. In general, cardiac cells that have genetically ablated CD38 show increased resistance to oxidative stress caused by IRI and, furthermore, suppress Ca^{2+} overload offering additional protection (71). Additionally, the absence of CD38 leads to sustained NAD^+/$NADP^+$ levels, which overall lead to sustained endothelial protection and functionally reduce arrhythmias during IRI (69). In addition to genetic ablation, there are several potent inhibitors of the CD38 pathway. 78c is the most common CD38 inhibitor and has had similar results to CD38 genetic ablation in that it maintains NAD^+/$NADP^+$ levels, reduces injury, and preserves cardiac function (67,73). Furthermore, a recent study examined the CD38 inhibitor MK-0159 (5). This inhibitor, as opposed to 78c, is available orally and has been shown to restore NAD^+, decrease secondary messengers that generate calcium, and most importantly protect the heart against IRI.

While we have discussed the possible benefits of CD38 inhibition, there are also detrimental effects. Deactivation of CD38 in the heart for a prolonged period of time can also have detrimental effects. Genetic CD38 deficiency can cause dysregulation of autophagy, leading to impaired clearance of type I collagen in the coronary arteries, and will ultimately cause plaque build-up and lead to atherosclerotic

disease (17). Furthermore, due to the lack of calcium-generating secondary messengers, cholesterol transport is also dysregulated and leads to accumulation of cholesterol in lysosomes, further facilitating atherosclerosis (74). Finally, it has been shown that a CD38 deficiency suppresses nuclear factor erythroid-2-related factor-2, promoting smooth muscle cell dedifferentiation, enhancing cell perforation, and again promoting atherosclerosis (75).

In future endeavors, it will be important to balance the function of CD38, as it appears to have a dual function: (I) mediating cell injury and elaborating inflammatory pathways to promote damage; and (II) ensuring that coronary arteries and vessels remain clear of plaque. To date, there have been no large animal studies or clinical trials evaluating the efficacy of CD38 inhibition and its effect on the heart during CPB. The efficacy of CD38 inhibition during IRI will need to be further substantiated in additional preclinical experiments as well as in human tissues.

Improving donor viability in thoracic transplantation

Transplantation is often the only cure for end-stage lung and heart disease. However, transplantation is limited by the available donor pool. Limited donor availability for lung and heart transplantation has led providers to explore the use of marginal donors, with promising results in both organs (76-78). However, these organs have significant limitations due to the substantial tissue injury that can result from various degrees of warm and cold ischemia before and during procurement. If not carefully controlled and accounted for, damage sustained from prolonged ischemic time and the subsequent IRI can lead to disastrous post-operative complications. In the heart, IRI manifests clinically as primary graft dysfunction (PGD) in heart allografts (79). Patients present with ventricular dysfunction (left, right, or both) with low cardiac output and hypotension (80,81). PGD affects around 20% of heart transplantation patients, with 1-year mortality rates ranging from 15–40% depending on severity (82). In the lungs, IRI also manifests clinically as PGD in lung allografts (83). Patients often have an increased oxygen demand, decreasing PaO_2:FiO_2 ratio, and interstitial opacities on imaging (84,85). The development of PGD has profound short- and long-term impacts on patient outcomes (86,87). Unfortunately, PGD is a relatively common adverse event that occurs in up to 40% of patients and significantly impacts recipient mortality and morbidity (86,88,89). Ultimately, the modulation of CD38 activity may help extend the viability of transplanted organs by reducing IRI in both the donor population during procurement and the recipient population during the transplant operation, and furthermore plays a role in immune modulation in general.

Immune modulation and antibody-mediated rejection

CD38's broad role in inflammation and cytokine release have obvious connections to immune modulation (90). CD38's role of NAD^+ modulation could have direct impacts on immune modulation leading to improved allograft survival and integrity. When supplemented with additional NAD^+ *in vivo*, Elkhal *et al.* were able to demonstrate mice undergoing transplantation were able to have prolonged allograft survival by promoting a robust systemic IL-10 response originating from $CD4^+$ T-helper cells (91). Inhibition of CD38 during the post-operative period following transplantation could have similar effects and promote allograft survival and decrease cell-mediated rejection. However, optimal dosing and treatment during are yet not known with the available CD38 inhibitors, nor effect in the post-transplantation period. This will be an area of future study and concern. In addition to the possibility of CD38 inhibition in the post-operative period, CD38 inhibition could have profound impacts on antibody mediated rejection. CD38 is expressed on the surface of a variety of immune cells to include plasma cells, and recently targeting these cells has been explored in transplantation (92). By using daratumumab (monoclonal CD38 inhibitor), Kwun *et al.* were able to show that pre-treating the donors with CD38 inhibitors significantly reduced anti-human leukocyte antigen (HLA) antibodies and lead to prolonged allograft survival. Overall, the modulation of CD38 could have profound impacts as an immunomodulator and future studies should be conducted in pre-clinical and clinical experiments to future validate these findings.

Heart transplantation

During heart transplantation it will be essential to focus on CD38's main effects: consumption of NAD^+, production of ROS and potent calcium secondary messengers. In addition to the studies already discussed, as well as important pathways to inhibit, the NLRP3-inflammasome will be particularly important to inhibit. As discussed previously, CD38's byproducts serve to activate the NLRP3-inflammasome (34-38), which leads to both pyroptosis and apoptosis. NLRP3 activation has been shown to significantly contribute to cardiac IRI (93,94). Specifically, in donation after circulatory death (DCD) heart transplantation models,

inhibiting the NLRP3-inflammasome has been shown to protect the donor allograft against pyroptosis and apoptosis alike (95). CD38 inhibition also has the potential to prevent the NLRP3-inflammasome formation and have similar effects on mechanisms of programmed cell-death. Clinically, this effect is also apparent as IL-18 (by-product of NLRP3 activation) concentrations at 24 hours post-transplant have been correlated with increasing severity of PGD (96).

During heart transplantation, the activation of certain types of CD38 could also be beneficial. Type II CD38 regulates extracellular adenosine from the consumption of NAD^+ (18). Purine synthesis and cell signaling is an important component of IRI as well as rejection during heart transplantation (97). Adenosine, in addition to vasodilatory and anti-inflammatory effects, has been shown to have several cardioprotective effects during IRI and transplant (98-100). Type II CD38 might exert a complementary effect to another known ectoenzyme that synthesizes adenosine, CD39 (18). CD39 overexpression has been shown to be effective in mitigating cardiac injury during IRI (101,102), and specifically in heart transplantation it has the ability to prevent platelet aggregation and improve the survival of heart allografts (103-105). The possible synergistic effects of CD38 and CD39 remain an underexplored area of research. During heart transplantation, it will be important to distinguish inhibition of type II and type III CD38. Inhibition of type III CD38 mitigates inflammatory cascades, while modulation of type II CD38 could offer protection to heart allografts.

Lung transplantation

Although CD38's role in heart-specific IRI has been firmly established, there is little data on its role in lung injury and insult. However, lung capillary networks are vast and CD38 is known to be highly conserved and expressed in the endothelium (3,12). Previous work examining the underlying molecular mechanisms of lung transplantation has highlighted several key pathways that overlap with the NAD^+/CD38/cADPR/Ca^{2+} axis. As the endothelium senses the cessation and resumption of blood flow, CD38 activates the resulting ROS production, intracellular Ca^{2+} influx, and ultimately the production and release of IL-1β. As discussed previously, excessive levels of intracellular Ca^{2+}, as well as ROS production, lead to pyroptosis and apoptosis, contributing to allograft damage, alveolar edema, and overall poor respiratory exchange (106). IL-1β plays an important role in recruiting recipient immune cells, most notably host classical monocytes (107). Monocytes are recruited to the donor allograft, break down the tight junctions of the endothelium, and perpetuate the recipient's immune response by attracting neutrophils that infiltrate the alveolar space to cause more damage and edema (108,109). Furthermore, CD38 is an important modulator of endothelin-1 (ET-1) activity, which is a vasoactive protein and marker of acute lung injury (110,111). During lung transplantation, high levels of ET-1 have been correlated with the development of PGD as well. Increased activity of CD38 leads to increased responsiveness to ET-1, while absence leads to decreased response and ultimately improved blood flow (112,113). Inhibition of CD38 can decrease the effects of ET-1 on potential allografts, and therefore improve blood flow and potentially mitigate PGD. The loss of endothelial protection, and thus the breakdown of this important barrier, leads to extravasation of neutrophils, edema, injury, and overall poor allograft function. Inhibition of CD38 would offer novel means of endothelial protection to prevent against IRI-related damage and rescue allografts during lung transplantation.

Therapeutic delivery

While modulation of CD38 could have vast clinical implications, the proper delivery method of these agents, pending application, is yet to be determined. Because CD38 exists as both as an endo- and ecto-form it can be advantageous to be able to inhibit both types. While type II can be more readily targeted due to its inherent nature, type III poses unique challenges. 78c (10) is a potent inhibitor of CD38, however due to its molecular structure is insoluble in water, and is difficult to deliver orally or intravenously at large quantities. Targeted drug delivery using nano-particles or extracellular vesicles (114) to house CD38 inhibitors could overcome this difficultly and effectively deliver therapeutics to inhibit type III CD38. These solutions could be delivered during CPB as part of the cardioplegia solution, or as an aerosolized solution in the ventilator. During transplantation, they could again be delivered in the cold-flush solution or in the preservation solution during cold storage. The most excited application in transplantation would be during machine perfusion (MP) of the heart or lung (115-118). MP is a dynamic assessment platform that offers transplant physicians the opportunity to evaluation potential allograft's suitability for transplantation. While the main advantage of MP currently is extended evaluation—therapeutic delivery and the possibility of resuscitation, repair and modifying allografts is the future of MP (119).

Limitations

There are limitations to this review. Since only PubMed indexed studies were included, invariably there were studies that perhaps met our inclusion criteria, however were not included in this work. In addition, because CD38 in the context of thoracic transplantation is a relatively new field of study, some of the inferences made must be further substantiated in pre-clinical as well as clinical studies.

Conclusions

CD38 is an important enzyme that is involved in many cellular functions. Intracellularly, it is most notably a NADase and a generator of potent Ca^{2+} generating secondary messengers. Ultimately, the release of these Ca^{2+} generating secondary messengers leads to the production of ROS, as well as activation of important mediators of programmed cell death. In the heart and during thoracic transplantation, this pathway is intimately involved in a wide variety of injury; namely the endothelium. In the heart, activation generally results in vasoconstriction, poor myocardial perfusion, and ultimately poor cardiac function. Parenthetically, however, CD38 activation prevents the accumulation of atherosclerotic disease. During transplantation, intracellular activation leads to infiltration of recipient innate immune cells, tissue edema, and ultimately PGD. Specifically, in heart transplantation, extracellular activation could be protective and improve allograft survival. Modulation of CD38 is a novel means to protect the heart and lung against IRI-related damage during CPB, as well as thoracic transplantation. These relationships are a promising area of research, and further study is needed in pre-clinical and clinical experiments in order to delineate a definitive connection between CD38 modulation and its use in thoracic transplant and CPB.

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Footnote

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Supplementary

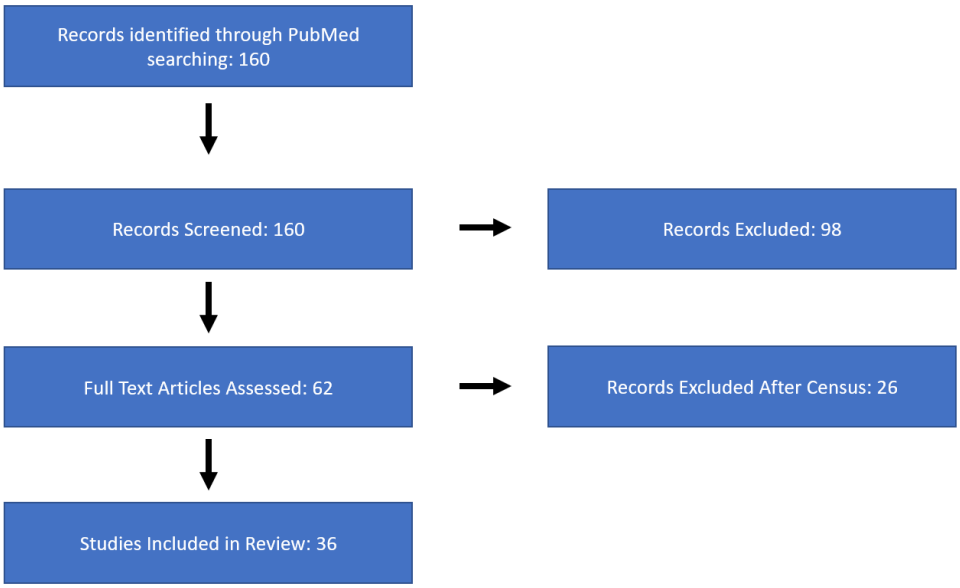

Figure S1 Flow diagram depicting our search methods.

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