



The Role of Interleukin-1 β in Destruction of Transplanted Islets

Cheng Chen^{1,2}, Pengfei Rong^{1,2}, Min Yang¹, Xiaoqian Ma², Zhichao Feng^{1,2}, and Wei Wang^{1,2} 

Cell Transplantation
Volume 29: 1–11
© The Author(s) 2020
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0963689720934413
journals.sagepub.com/home/ccl


Abstract

Islet transplantation is a promising β -cell replacement therapy for type 1 diabetes, which can reduce glucose lability and hypoglycemic episodes compared with standard insulin therapy. Despite the tremendous progress made in this field, challenges remain in terms of long-term successful transplant outcomes. The insulin independence rate remains low after islet transplantation from one donor pancreas. It has been reported that the islet-related inflammatory response is the main cause of early islet damage and graft loss after transplantation. The production of interleukin-1 β (IL-1 β) has considered to be one of the primary harmful inflammatory events during pancreatic procurement, islet isolation, and islet transplantation. Evidence suggests that the innate immune response is upregulated through the activity of Toll-like receptors and The NACHT Domain-Leucine-Rich Repeat and PYD-containing Protein 3 inflammasome, which are the starting points for a series of signaling events that drive excessive IL-1 β production in islet transplantation. In this review, we show recent contributions to the advancement of knowledge of IL-1 β in islet transplantation and discuss several strategies targeting IL-1 β for improving islet engraftment.

Keywords

islet transplantation, graft dysfunction, IL-1 β , Toll-like receptors, NLRP3 inflammasome

Introduction

Islet transplantation is one of the most promising ways to cure type 1 diabetes by achieving sustained insulin independence and good glycemic control^{1,2}. However, clinical islet transplantation faces two major problems before large-scale application: efficacy of restoring insulin production and donor shortages. A successful islet transplantation usually requires multiple pancreatic donors and multiple islet infusions, because islets are particularly vulnerable in the first few days after transplantation³. Early stress damage to islet transplantation by various stress stimuli such as inflammation, hypoxia, and immune response has hindered long-term good results of islet transplantation^{4,5}. Studies have shown that the loss of islets after transplantation is mainly due to inflammatory events, which occur before adaptive immune-induced rejection, involving the production of cytokines, platelet activation, coagulation and complement system activation, and recruitment of immune cells⁶. Innate immunity is considered to be one of the most important factors affecting early islet loss⁷. The innate immune system is primarily regulated by Toll-like receptors (TLRs) and NOD-like receptors (NLRs), which are pattern recognition receptors that recognize specific danger-associated molecular patterns

(DAMPs) or pathogen-associated molecular patterns (PAMPs) and activate nonspecific but powerful inflammatory responses⁸. DAMPs and PAMPs range from bacterial products, adenosine triphosphate (ATP), viruses, and mitochondrial DNA, to granular substances such as crystals and amyloids. This response involves the production of cytokines such as interleukin-1 β (IL-1 β), which regulate the inflammatory cell recruitment to islets and mediate cytotoxic damage to β cells^{9,10}. The amount of pro-inflammatory cytokine IL-1 β is upregulated when islets are exposed to warm/cold ischemic stresses during pancreas procurement and to mechanical, enzymatic, and hypoxic conditions during islet

¹ Cell Transplantation and Gene Therapy Institute, The Third Xiangya Hospital of Central South University, Changsha, Hunan, China

² Department of Radiology, The Third Xiangya Hospital of Central South University, Changsha, Hunan, China

Submitted: March 22, 2020. Revised: May 11, 2020. Accepted: May 21, 2020.

Corresponding Author:

Wei Wang, Cell Transplantation and Gene Therapy Institute, The Third Xiangya Hospital of Central South University, Tongzipo Road 138, Yuelu District, 410013 Changsha City, Hunan Province, China.
Email: wang_wei@csu.edu.cn



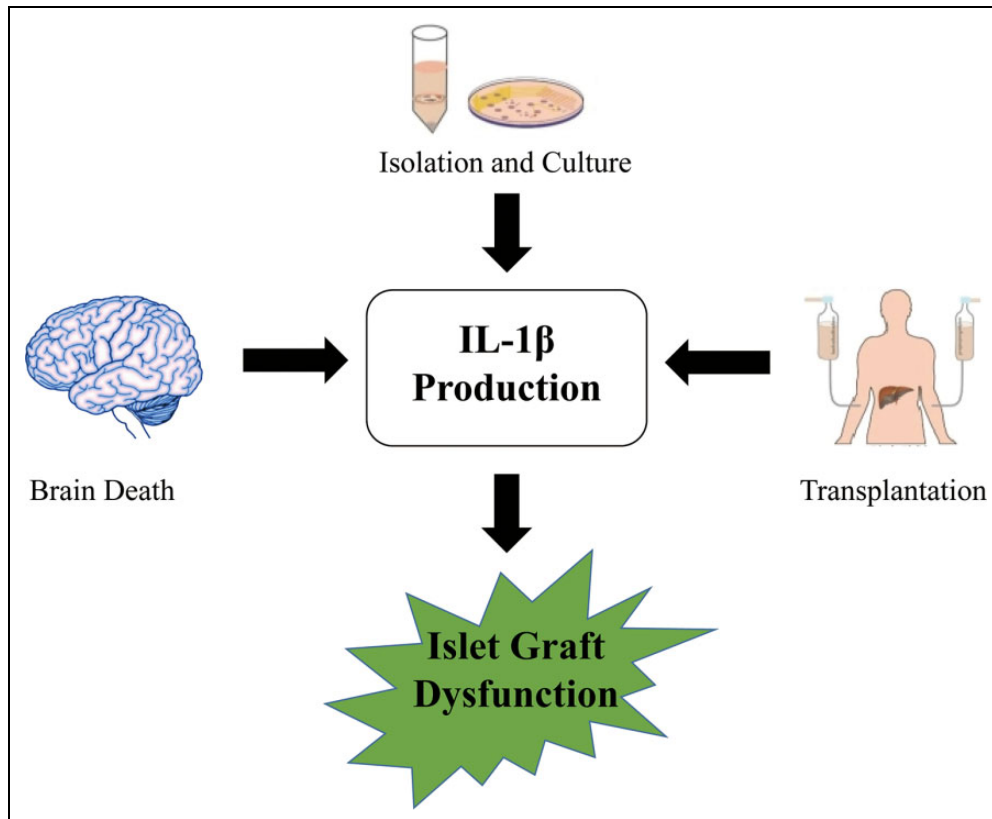


Figure 1. IL-1 β increased during pancreas procurement, islet isolation/culture, and islet transplantation. IL-1 β : interleukin-1 β .

isolation and culture (Fig. 1). Moreover, islet resident macrophages, Kupffer cells, and neutrophils around the transplantation site can secrete IL-1 β ¹¹. Islet grafts are exposed to inflammatory damage similar to the early stages of autoimmune diabetes¹², and IL-1 β is one of the key factors in the progression of islet graft failure^{13–17}.

The signaling pathway from TLR activation to mature IL-1 β secretion is divided into two steps. First, intracellular signal transduction of TLRs after binding to a ligand is mediated by adaptors such as myeloid differentiation factor 88 (MyD88)¹⁸. Subsequent activation of the nuclear factor- κ B (NF- κ B) in the intracellular signaling pathway increases the transcription of the IL-1 β gene to encode pro-IL-1 β , thereby increasing intracellular pro-inflammatory factor levels. Second, the protein processing of pro-IL-1 β is carried out by a complex called inflammasome. Inflammasomes are multiprotein complexes that are activated during infection, inflammation, and autoimmune diseases. These inflammasomes comprise receptors from either the NLR or the ALR family, an adaptor molecule Apoptosis-associated Speck-like protein Containing a caspase recruitment domain (ASC) and the procaspase-1. The NACHT Domain-Leucine-Rich Repeat and PYD-containing Protein 3 (NLRP3) inflammasome has been frequently studied compared to other inflammasomes. The NLRP3 inflammasome comprises a

cytoplasmic receptor NLRP3 and ASC that mediates caspase-1-dependent maturation of the pro-inflammatory cytokines IL-1 β ¹⁹ (Fig. 2). It is worth noting that although there are pathways other than TLRs such as the ATP receptor P2X7 to cause IL-1 β production, and other inflammasomes that activate caspase-1, such as NLRP1 and NLRP4, in this review we highlight the roles of the TLRs and NLRP3 inflammasome in islet transplantation. In recent years, researches on TLRs and NLRP3 inflammasome in islet transplantation as well as other organ transplantations have become increasingly important²⁰. A systematic understanding of the role of IL-1 β , TLRs, and NLRP3 in islet transplantation may improve islet transplantation outcome.

IL-1 β and Islet Transplantation

IL-1 β in Pancreas Donors

Although most pancreas and islet grafts are recovered from heart-beating brain-dead (BD) donors, which have much better outcomes than organs from non-heart-beating donors, the islet cells are still damaged from inflammatory events within the donor. Brain death is characterized by extensive cortical necrosis, which can stimulate the production of pro-inflammatory cytokines in a variety of cell types, the so-called “cytokine storm” in BD donors including IL-1 β ^{21–23}. The

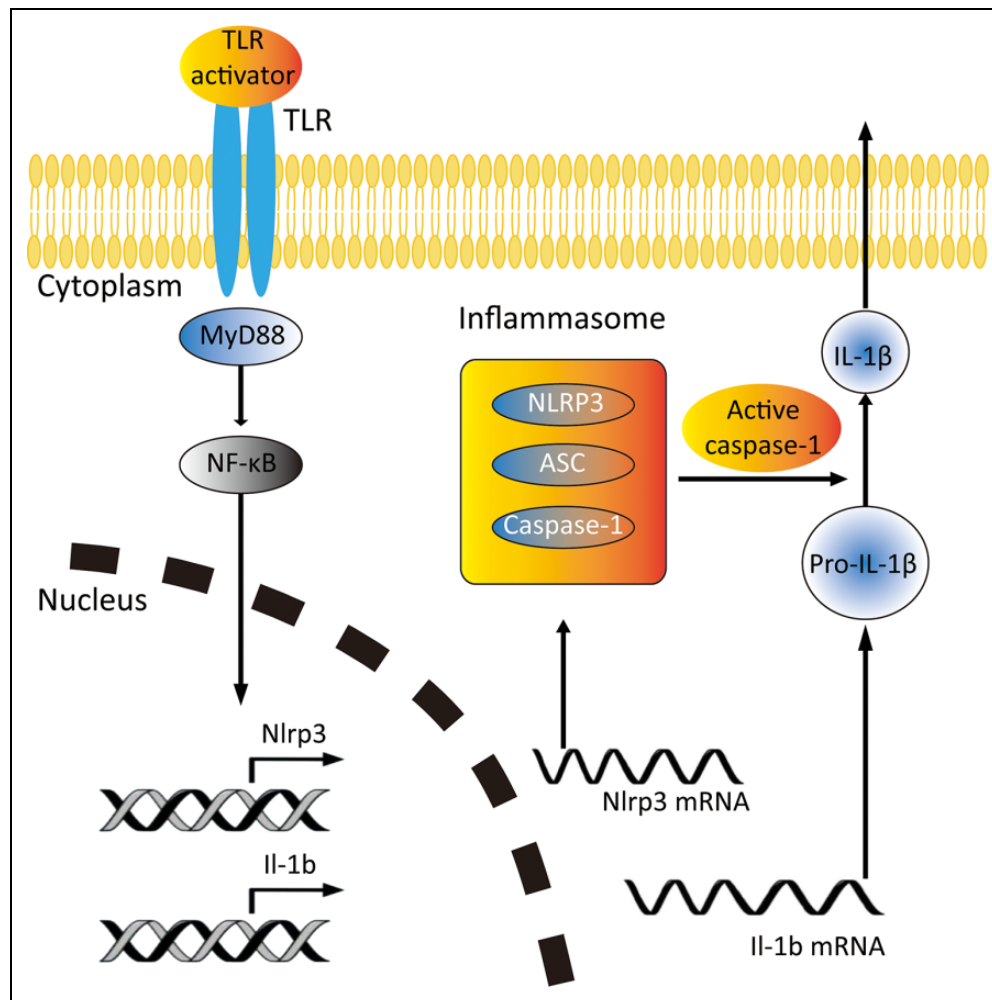


Figure 2. Schematic of TLR and NLRP3 inflammasome activation and IL-1 β secretion in islet transplantation. IL-1 β : interleukin-1 β ; NLRP3: NACHT Domain-Leucine-Rich Repeat and PYD-containing Protein 3; TLR: Toll-like receptor.

release of these pro-inflammatory cytokines has been shown to be associated with brain death, greatly reducing islet yield, functionality, viability, and engraftment post-transplantation²³. It has been demonstrated that macrophages infiltrate islets during brain death, and that macrophage-related inflammatory cytokines such as IL-1 β and IL-6 in islets are induced by brain death²⁴.

Recent studies have shown ways to improve islet graft function by inhibiting the BD inflammatory mediator IL-1 β before inducing BD. In a BD rat model, administration of exendin-4 to BD donors can increase islet vitality and glucose-stimulated insulin secretion with a significant decrease in IL-1 β expression in the pancreas²⁵. A selective neutrophil elastase inhibitor, transfusing sivelestat sodium, was shown to decrease IL-1 β level and increase islet yield, protect islet function and quality, and inhibit hypercytokinemia-mediated β -cell death in a BD rat model²⁶. In a BD nonhuman primate donor model, donor pretreatment with IL-1 receptor antagonist (IL-1Ra) can reduce inflammation by reducing intracellular IL-1 β and

improve islet survival and engraftment in mice transplanted with minimal islet²⁷.

IL-1 β in Islet Isolation and Culture

During pancreas digestion and islet purification, islets are exposed to mechanical, enzymatic, ischemic, and osmotic stress. It is well known that enzymes and mechanical stress can induce inflammatory mediators in the islets, such as IL-1 β . Gene array study has shown upregulation of genes related to inflammation, apoptosis, cell growth, and angiogenesis immediately after isolation²⁸. In that study, IL-1 β gene expression was reported to be upregulated by 10 times in islets cultured for 2 days. In cultured adult porcine islets, the presence of mRNA for IL-1 β was detected constantly for 11 days and slightly increased during the culture period²⁹. It is worth noting that, in the context of clinical islet transplantation, human serum albumin is used instead of fetal bovine serum due to safety issues in using animal-derived materials. Serum deprivation during *in vitro* culture before

transplantation results in islet amyloid polypeptide (IAPP) induced IL-1 β secretion and impaired islet vitality and function³⁰. Human islets precultured with IL-1Ra showed significant reduction of the pro-inflammatory mediators IL-1 β and IL-6 compared to the basal levels, which obviously improved engraftment after transplantation^{30,31}.

IL-1 β in Inflammatory Response After Islet Transplant

IL-1 β is among the key mediators of early islet dysfunction and destruction after islet transplantation, and its role in islet dysfunction has been extensively studied¹⁵. IL-1 β has received special attention due to its important role in the organization and amplification of acute inflammatory responses to tissue damage³². In the pancreas, the production and secretion of IL-1 β is mainly caused by activated macrophages, neutrophils, endothelial cells, and β cells in islets³³. Nonspecific inflammation increases IL-1 β at the transplant site and affects early graft failure³⁴. A syngeneic rat islet transplantation model demonstrated that the gene expression of IL-1 β in the islet graft of hyperglycemia rats was significantly increased on the first day after transplantation, compared with the islets before transplantation³⁵. On the third day after transplantation, a large number of macrophages existed around the islet tissue and necrotic area, and the apoptosis of β cells was significantly increased compared with the freshly isolated islets. In line with that report, Cardozo et al. found the expression of IL-1 β gene in Balb/c islet allograft was detected 8 h after transplantation³⁶. In addition, a study suggested a significant increase in IL-1 β levels after total pancreatic allograft ischemia-reperfusion injury³⁷. Experimental models have shown that inhibition of IL-1 β release can reduce islet injury, and circulating anti-IL-1 β antibodies can protect islets³⁸. Administration of sodium salicylate to inhibit IL-1 β -mediated induction of COX-2 can also improve function of pancreatic islets³⁹.

IL-1 β in Stem Cell-Derived β Cells and Capsules or Devices Encapsulating Islet Cells

Due to islet donor shortages, works on finding alternative resources for β cells are in progress. The development of stem cell-derived β cells such as human embryonic stem cells (hES) and induced pluripotent stem cells (iPSC)-derived insulin-producing cells is expected to offer the solutions. Although several teams have successfully manufactured insulin-secreting cells from hES and iPSC, clinical translation requires new solutions to solve the safety problems regarding teratoma formation and immune rejection⁴⁰. Moreover, stem cell-derived β cells are “immature” that may be more vulnerable to inflammatory response such as IL-1 β ⁴¹. These limitations have led to the invention of immune-protected encapsulated devices to contain cells in the device and protect them from attacks of the immune system after transplantation. Many side effects of immunosuppressive agents, including infections, malignancies,

worsening renal function, and suppression of islet function, can be overcome by these devices⁴². Studies show capsules or devices encapsulating islet cells can resist to IL-1 β damage in the protection of biomaterials⁴³. However, the main issues regarding the mass transport of nutrients and oxygen, insulin secretion kinetics, and xenobiotic reactions to encapsulated devices remain to be resolved. Lack of nutrients and oxygen likely results in islet IL-1 β production as evidence showed *in vitro*³⁰. In summary, these data indicate that more studies are still required in the field of stem cell-derived β cells and immunoprotective encapsulation strategies.

The Effect of IL-1 β on β Cells

Islet β cells are susceptible to IL-1 β stimulation during the process of islet transplantation. Through a cascade of intracellular events, low-dose IL-1 β leads to a decrease in the biosynthesis and secretion of glucose-stimulated insulin, whereas high-dose IL-1 β leads to apoptosis in islets⁴⁴. The binding of IL-1 β to the IL-1 β receptor (IL-1 β R) on the surface of islet cells is the initial step in a series of events leading to gene transcription. After IL-1 β interacts with IL-1 β R, the receptor undergoes a conformational change, allowing the accessory protein of the IL-1 receptor to be coupled, and subsequently forming a multiprotein complex involving Toll-interacting proteins and the MyD88⁴⁵. This binding results in the activation of tumor necrosis factor receptor-associated factor 6 (TRAF6) by IL-1 receptor-associated kinase (IRAK)⁴⁶. TRAF6 is a type 3 enzyme ubiquitin ligase that mediates the activation of the inhibitor of nuclear factor kappa B kinase (I κ K) by ubiquitination, and active I κ K phosphorylates the NF- κ B inhibitor (I κ B), releasing the inhibitory effect on NF- κ B and transferring it from the cytoplasm to the nucleus of islet β cell⁴⁷. Traditionally, NF- κ B has been broadly referred to as the heterodimer p50/p65 (p50/RelA), an apoptosis-regulating gene⁴⁸. Upon entry into the nucleus, NF- κ B induces the expression of inducible nitric oxide synthase in islet β cell. This enzyme acts as a catalyst for L-arginine to produce NO, which is capable of reacting with DNA fragments and prosthetic groups present in transcription factors, and reduces glucose oxidation, oxygen consumption, and ATP synthesis, therefore reduces insulin synthesis⁴⁹. In addition, NF- κ B signaling can lead to transcriptional activation of priming cytokines/chemokines (such as IL-6, MCP-1, and IL-8), which are detrimental to islets¹⁵. IL-1 β can also lead to downregulation of glucose transporter 2 (GLUT2) and glucokinase mRNA expression, enzymes for glucose transport, and phosphorylation in islets⁵⁰. GLUT2 is an important component of the glucose response apparatus in pancreatic β cells, and downregulation of GLUT2 impairs the function of islets to detect elevated serum glucose levels and respond precisely⁵¹. Finally, in addition to the adverse effects of IL-1 β on β cell viability and function, this cytokine also has a negative impact on β cell replication and quality^{52,53}. Overproduction of IL-1Ra increases β cell replication and islet graft mass,

and reduces the number of β cells needed to achieve normoglycemia after islet transplantation.

Evidence for Possible Mechanisms of IL-1 β Upregulation in Islet Transplantation

Toll-like Receptors

As important innate immune receptors, TLRs are type 1 transmembrane glycoprotein receptors containing leucine-rich repeat motifs that bind various ligands, as well as a highly conserved cytoplasmic domain for the binding of downstream adaptor molecules. TLRs recognize PAMPs, such as bacterial cell membrane lipids, viral double-stranded RNA and DNA oligonucleotides, and can also be activated by host-derived DAMPs such as high mobility groups Box 1 (HMGB1) and heat shock proteins⁵⁴. When islet grafts are isolated and transplanted, many exogenous and endogenous TLR ligands are released⁵⁵. Upon binding to their associated ligand, the TLRs recruit intracellular signaling molecules (e.g., MyD88, Toll interacting protein, IRAK, and TRAF6), resulting in activation of c-Jun N-terminal kinase, p38, and NF- κ B signaling pathways⁵⁶. Through these signaling pathways, TLRs activate transcription factors, thereby increasing the expression of various pro-inflammatory cytokines and chemokines⁵⁷. Although TLRs are most commonly associated with infectious diseases, they have recently been associated with noninfectious diseases such as diabetes⁵⁸. Surgical trauma and ischemia-reperfusion injury result in the release of endogenous TLR ligands can also activate TLRs to mediate the inflammatory response⁵⁹. The expression of TLRs in islets has been studied at the message and protein levels in many studies. TLR 2, 3, and 4 mRNA are readily detected in C57BL/6 mice and human islets⁶⁰, and studies have reported TLR2 and TLR4 expression in rat INS-1 and BRIN-BD11 and mouse MIN6 β cell lines^{58,61,62}.

The role of TLRs in islet transplantation has been well studied. Mouse syngeneic islet transplantation shows that deletion of donor TLR4, rather than deletion of transplant recipient TLR4, can reduce early post-transplant inflammatory response and increase graft viability. Compared with wild type (WT) islet engrafted in the liver, the TLR4^{-/-} islet grafts have significant lower IL-1 β expression⁶³. In the mouse allogeneic islet transplantation model, TLRs in both donor islets and recipients are involved in allograft rejection. In that study, the absence of MyD88 in either the donor or the recipient can reduce perigraft infiltration of inflammatory cells and improve transplant outcome⁶⁴. Another group shows that islet transplantation failure can be triggered by TLR2 and TLR4 signaling, and HMGB1 is a possible early mediator. Subsequent downstream signaling leads to inflammation in the islets, followed by T cell-mediated graft destruction^{65,66}. In addition, islet isolation can lead to increased expression of TLR4, which can be reduced by

prior exposure of donor islets to carbon monoxide, thereby prolonging the survival of allogeneic islets⁶⁷.

In islet xenotransplantation, TLRs activation in porcine islets induces pro-inflammatory and procoagulant responses leading to xenograft rejection⁶⁸. Studies also show that TLR is an important signal for macrophage-mediated pancreatic islet xenograft recognition and rejection. Macrophages exposed to porcine islets have significant higher levels of TLRs gene expression compared with exposure to allogeneic islets⁶⁹. Loss of MyD88 in TLR signaling also leads to impaired macrophage activation after porcine islet xenografts⁶⁹. Although a number of studies have shown the role of TLR signaling in islet transplantation, its significance for islet graft loss remains controversial. Schmidt et al. found that porcine islet xenograft rejection still exists in MyD88^{-/-} mice⁷⁰. Hutton et al. reported that the absence of TLR4, MyD88, and TLR adaptor molecule Ticam-1 did not significantly improve graft survival compared with WT controls⁷¹. More precise understanding of the TLRs in islet transplantation is warranted.

NLRP3 Inflammasome

In recent years, researchers have found another family involved in innate immunity: the NLRs. The NLR family has three distinct subfamilies: the NOD, NLRP, and IPAF subfamilies, encoded by at least 22 human genes⁵⁶. As mentioned earlier, the NLRP3 inflammasome is a protein complex comprising NLRP3, ASC, and caspase-1. NLRP3 acts as a receptor that senses the exogenous pathogen and endogenous danger signal in the cytoplasm. It consists of 11 leucine repeats at the C-terminus, a NACHT domain in the middle, and a Pyrin domain (PYD) at the N-terminus. Activation of NLRP3 leads to oligomerization and recruitment of ASC and pro-caspase-1, as well as autocleavage and activation of caspase-1⁷². The adaptor protein ASC has a molecular weight of 21.5 kDa and has 195 amino acid residues. It is an important linker protein that consists of the PYD and the Caspase recruitment domain, connecting NLRP3 upstream and caspase-1 downstream. Caspase-1, also known as IL-1 β converting enzyme, is an effector protein of the NLRP3 inflammasome and is responsible for cleaving inactive pro-inflammatory cytokines pro-IL-1 β and pro-IL-18 to mature IL-1 β and IL-18. There are several PAMPs, DAMPs, and environmental stimulus that can activate NLRP3⁷³. Endogenous danger signals such as ATP, uric acid crystals, cholesterol crystals, reactive oxygen species, β -amyloid, extracellular matrix components, and lysosomal lysing components, as well as many kinds of exogenous factors such as viruses, bacteria, and fungi can cause assembly and activation of NLRP3 inflammasome.

Studies have shown that elevated blood glucose is associated with activation of NLRP3 inflammasome in islets, resulting in the production of mature IL-1 β ⁷⁴⁻⁷⁶. However, the relative contribution of endocrine cell types and resident islet macrophages to islet IL-1 β secretion was not

investigated in these studies. Because TLRs and IL-1 β are upregulated in islet transplantation⁷⁷, NLRP3 inflammasome is likely to be activated in this case. Recently, our team found that hypoxia can enhance LPS-induced inflammatory responses by upregulating NLRP3 expression in mouse β cells⁷⁸. Notably, hypoxia is one of the biggest challenges for the islet graft after islet transplantation especially in encapsulating islet cells. We and another group showed in human and porcine islets that NLRP3 inflammasome is expressed and regulated, and hypoxia can increase the gene expression of NLRP3 and pro-IL-1 β and induce production of IL-1 β and caspase-1^{79,80}. Another study shows NLRP3-deficient islets have *ex vivo* functions and are resistant to hypoxia-induced cell death, compared with wild-type islets⁸¹. Besides, evidences show that knocking down ASC in β cells can improve IL-1 β -induced cell death and reduce cytokine-induced NO production⁸². These studies suggest islet expressing NLRP3 inflammasome may play a role in graft injury after islet transplantation; however, its role in islet transplantation *in vivo* has yet to be confirmed.

NLRP3 inflammasome expressed in both islet resident and infiltrated macrophages and other immune cells may significantly contribute to graft dysfunction after islet transplantation. Islet β cells can produce IAPP while secreting insulin. IAPP aggregates were detected in clinical pancreatic islet grafts and it can lead to recurrence of hyperglycemia after transplantation^{83–85}. Its potential role in clinical islet transplant failure has been reviewed elsewhere recently⁸⁶. In macrophages, IAPP acts as a potent second signal to activate NLRP3 inflammasome, resulting in the secretion of IL-1 β ⁸⁷. In diabetic mice transplanted with human IAPP transgenic islets, the number of macrophages increased, and these macrophages were inhibited by exogenous IL-1Ra¹³. In the liver, which is the site of clinical islet transplantation, the Kupffer cells express abundant NLRP3 inflammasome and contribute to acute liver injury⁸⁸. This may destruct the islets after transplantation. These studies indicate that the IL-1 β production of immune cells through NLRP3 inflammasome activation in transplant site can damage the β cells.

Therapeutic Opportunity Targeting IL-1 β Biology for Islet Graft Dysfunction

Therapeutics targeting the IL-1 system has been studied extensively for islet graft protection. The ligands and receptors of the IL-1 offer various opportunities for intervention such as IL-1Ra, IL-1RTI-IL-1RAcP fusion protein (IL-1 trap), and soluble IL-1 receptor type II (sIL-1RII). IL-1Ra is an endogenous IL-1 inhibitor that binds to IL-1R1 and blocks the recruitment of IL-1 R accessory protein (IL-1RAcP), thereby effectively blocking the activation of the IL-1 receptor⁸⁹. The presence of IL-1Ra in human serum from healthy subjects can prevent systemic effects of moderate upregulation of IL-1 release caused by limited injury. Under homeostatic conditions, there is an equilibrium between IL-1 β and IL-1Ra^{90,91}. Therefore, when the IL-

1Ra content is lowered, there is a potential activity of IL-1 β leading to downstream effects. The use of this property of IL-1Ra to develop synthetic IL-1Ra and IL-1 trap as anti-inflammatory tools was approved for the treatment of certain types of arthritis in clinic. Moreover, clinical studies have shown that commercially available IL-1Ra (Anakinra) and IL-1 neutralizing antibody (Canakinumab) can reduce insulin requirements and glycated hemoglobin levels in patients with type 2 diabetes^{92,93}. Recently, these relatively new compounds have been studied more frequently in islet transplantation^{14,15,30,94,95}.

Treatment of rat islet cells with anakinra prevents pro-inflammatory cytokine-induced cell death⁹⁶. After transplantation of pancreatic islets from hIAPP-expressing transgenic mice into diabetic NOD/SCID mice, implantation of an anakinra-containing micro-osmotic pump in recipients attenuates islet amyloid-induced pro-inflammatory cytokine release and islet graft dysfunction¹³. Donor pretreatment with anakinra reduces inflammation and improves viability, mitochondrial membrane polarity, and islet engraftment in mice transplanted with minimal islet mass²⁷. In addition, anakinra can synergize with other anti-inflammatory drugs to prevent islet graft damage. Anakinra enhances the protective effect of the tumor necrosis factor alpha inhibitor etanercept on human islets transplanted in mice⁹⁷. The combination of anakinra and etanercept significantly improved islet engraftment compared to monotherapy-treated mice or controls⁹⁸. In a clinical trial of total pancreatectomy with islet autotransplantation, patients received anakinra and etanercept treatment from the day of transplantation to day 7, showed improved islet engraftment and better transplant outcomes¹⁵. Pretreatment with anakinra and tocilizumab (a monoclonal IL-6 receptor antibody) significantly improved human islet function compared with controls³¹. Other strategies that increase IL-1Ra can also protect post-transplant islets. In mouse allogeneic islet transplantation, α 1-antitrypsin exerts allograft-protective activity through the induction of IL-1Ra both in islets and macrophages⁹⁹. IL-1Ra expressing mesenchymal stem cells (MSCs) can mitigate the cytotoxicity of IL-1 β in the islets and improve the transplant outcome^{100,101}. IL-1 trap is an alternative choice to block IL-1 signaling. The use of IL-1 trap counteracts the destruction of islet cells and prolongs the survival of transplanted islets in diabetic NOD mice⁹⁵. Besides, soluble IL-1 inhibitor sIL-1RII significantly improved the rates of graft survival in anti-CD4 monoclonal antibody treated diabetic NOD mice¹⁰². These strategies that directly block the IL-1 system showed potential in improving islet transplant outcome. However, more randomized controlled trials in humans need to be conducted in the future, especially IL-1 inhibiting strategies in the isolation bath of the pancreas and in the islet extraction process.

In addition to IL-1-targeted strategies, TLRs and NLRP3 also present important therapeutic opportunities in the prevention of islet graft dysfunction. Blocking TLR4 using a species-specific anti-TLR4 monoclonal antibody

significantly increased the survival rate in both syngeneic and allogeneic islet transplantation¹⁰³. Early blockade of TLR4 by TLR4 antagonists protects islets from sustained sterile inflammation-mediated stress during islet isolation and promotes good transplant outcomes¹⁰⁴. A cell permeable peptide PTD-dnTLR4 blocks TLR4 signaling in both macrophages and β cells, and prolongs the survival of allografts by inhibiting inflammation and macrophage infiltration⁷⁷. TAK-242, a small molecular inhibitor of TLR4, was recently shown to protect islet grafts. Localized drug delivery of TAK-242 within the islets in transplantation site can promote satisfied transplant outcomes¹⁰⁵. ODN 1585, a CpG oligonucleotide TLR9 agonist, can enhance the expansion of IL-22 producing CD3-NK1.1+ cells in the liver, resulting in IL-22-mediated prolonged allograft survival and increased islets function¹⁰⁶. Therapeutics targeting NLRP3 in islet transplantation are rarely reported so far. Glyburide, a therapy currently in clinic to treat T2D, can inhibit the NLRP3 inflammasome resulting in decreased IL-1 β levels in human islet treated with LPS+ ATP⁷⁹. Our group have reported that human umbilical cord-derived MSCs can protect porcine islets from hypoxia-induced cell death. This effect is partially mediated by decreasing expression of NLRP3^{80,107}. Together, strategies targeting TLRs-NLRP3-IL-1 β pathway showed promising improvement in experimental islet transplantation models. But further clinical trial is needed to confirm its effectiveness.

Conclusions

Early islet graft dysfunction and loss of islet mass occurs within a few days after transplantation. IL-1 β is one of the most important cytokine mediators of inflammation and plays an important role in the pathogenesis of islet graft dysfunction and may represent an early inflammatory marker of graft failure. Since TLRs and NLRP3 inflammasome has been implicated in the mechanism of islet graft loss, the effect of TLRs and NLRP3 on graft dysfunction is likely to be mediated by IL-1 β . Nevertheless, there are still many unsolved questions about the role of TLRs and NLRP3 inflammasome in the destruction of pancreatic islet cells during islet transplantation. Meanwhile, IL-1 inhibitor used in clinical studies to date is not enough to fully reduce the insulin needs indicates other signal pathways may also participate the islet destruction. A further understanding of the crosstalk between TLRs-NLRP3-IL-1 β pathway and other signal pathways, and the therapeutic options that target this process may improve the outcome of islet transplantation.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This

work was supported by the National Natural Science Foundation of China (Grant Nos: 81201171, 81671752, 81471715, and 81771827), Hunan Provincial Science and Technology Department major project (Grant No.: 2018SK1020), and Natural Science Foundation of Hunan Province, China (Grant No.: 2017JJ3423).

ORCID iD

Wei Wang  <https://orcid.org/0000-0002-9795-2563>

References

- Shapiro AM, Lakey JR, Ryan EA, Korbitt GS, Toth E, Warnock GL, Kneteman NM, Rajotte RV. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *N Engl J Med*. 2000;343(4):230–238.
- Shapiro AM, Ricordi C, Hering BJ, Auchincloss H, Lindblad R, Robertson RP, Secchi A, Brendel MD, Berney T, Brennan DC, Cagliero E, et al. International trial of the Edmonton protocol for islet transplantation. *N Engl J Med*. 2006;355(13):1318–1330.
- Vantyghem MC, de Koning EJP, Pattou F, Rickels MR. Advances in beta-cell replacement therapy for the treatment of type 1 diabetes. *Lancet*. 2019;394(10205):1274–1285.
- Linn T, Schmitz J, Hauck-Schmalenberger I, Lai Y, Bretzel RG, Brandhorst H, Brandhorst D. Ischaemia is linked to inflammation and induction of angiogenesis in pancreatic islets. *Clin Exp Immunol*. 2006;144(2):179–187.
- Lai Y, Schneider D, Kiszun A, Hauck-Schmalenberger I, Breier G, Brandhorst D, Brandhorst H, Iken M, Brendel MD, Bretzel RG, Linn T. Vascular endothelial growth factor increases functional beta-cell mass by improvement of angiogenesis of isolated human and murine pancreatic islets. *Transplantation*. 2005;79(11):1530–1536.
- Lai Y, Chen C, Linn T. Innate immunity and heat shock response in islet transplantation. *Clin Exp Immunol*. 2009;157(1):1–8.
- von Zur-Muhlen B, Lundgren T, Bayman L, Berne C, Bridges N, Eggerman T, Foss A, Goldstein J, Jenssen T, Jorns C, Morrison Y, et al. Open randomized multicenter study to evaluate safety and efficacy of low molecular weight sulfated dextran in islet transplantation. *Transplantation*. 2019;103(3):630–637.
- Price AE, Shamardani K, Lugo KA, Deguine J, Roberts AW, Lee BL, Barton GM. A map of toll-like receptor expression in the intestinal epithelium reveals distinct spatial, cell type-specific, and temporal patterns. *Immunity*. 2018;49(3):560–575.
- Donath MY, Dinarello CA, Mandrup-Poulsen T. Targeting innate immune mediators in type 1 and type 2 diabetes. *Nat Rev Immunol*. 2019;19(12):734–746.
- Mathis D, Vence L, Benoist C. Beta-cell death during progression to diabetes. *Nature*. 2001;414(6865):792–798.
- Kanak MA, Takita M, Kunnathodi F, Lawrence MC, Levy MF, Naziruddin B. Inflammatory response in islet transplantation. *Int J Endocrinol*. 2014;2014:451035.
- Filippi CM, von Herrath MG. Islet beta-cell death - fuel to sustain autoimmunity? *Immunity*. 2007;27(2):183–185.

13. Westwell-Roper C, Dai DL, Soukhatcheva G, Potter KJ, van Rooijen N, Ehses JA, Verchere CB. IL-1 blockade attenuates islet amyloid polypeptide-induced proinflammatory cytokine release and pancreatic islet graft dysfunction. *J Immunol*. 2011;187(5):2755–2765.
14. Citro A, Cantarelli E, Pellegrini S, Dugnani E, Piemonti L. Anti-inflammatory Strategies in intrahepatic islet transplantation: a comparative study in preclinical models. *Transplantation*. 2018;102(2):240–248.
15. Naziruddin B, Kanak MA, Chang CA, Takita M, Lawrence MC, Dennison AR, Onaca N, Levy MF. Improved outcomes of islet autotransplant after total pancreatectomy by combined blockade of IL-1beta and TNFalpha. *Am J Transplant*. 2018;18(9):2322–2329.
16. Sandberg JO, Eizirik DL, Sandler S. IL-1 receptor antagonist inhibits recurrence of disease after syngeneic pancreatic islet transplantation to spontaneously diabetic non-obese diabetic (NOD) mice. *Clin Exp Immunol*. 1997;108(2):314–317.
17. Park YJ, Warnock GL, Ao Z, Safikhani N, Meloche M, Asadi A, Kieffer TJ, Marzban L. Dual role of interleukin-1beta in islet amyloid formation and its beta-cell toxicity: implications for type 2 diabetes and islet transplantation. *Diabetes Obes Metab*. 2017;19(5):682–694.
18. Ospelt C, Gay S. TLRs and chronic inflammation. *Int J Biochem Cell Biol*. 2010;42(4):495–505.
19. Schroder K, Zhou R, Tschopp J. The NLRP3 inflammasome: a sensor for metabolic danger?. *Science*. 2010;327(5963):296–300.
20. Diamond JM, Wigfield CH. Role of innate immunity in primary graft dysfunction after lung transplantation. *Curr Opin Organ Transplant*. 2013;18(5):518–523.
21. Kusaka M, Pratschke J, Wilhelm MJ, Ziai F, Zandi-Nejad K, Mackenzie HS, Hancock WW, Tilney NL. Activation of inflammatory mediators in rat renal isografts by donor brain death. *Transplantation*. 2000;69(3):405–410.
22. Wilhelm MJ, Pratschke J, Beato F, Taal M, Kusaka M, Hancock WW, Tilney NL. Activation of the heart by donor brain death accelerates acute rejection after transplantation. *Circulation*. 2000;102(19):2426–2433.
23. Contreras JL, Eckstein C, Smyth CA, Sellers MT, Vilatoba M, Bilbao G, Rahemtulla FG, Young CJ, Thompson JA, Chaudry IH, Eckhoff DE. Brain death significantly reduces isolated pancreatic islet yields and functionality *in vitro* and *in vivo* after transplantation in rats. *Diabetes*. 2003;52(12):2935–2942.
24. Toyama H, Takada M, Suzuki Y, Kuroda Y. Activation of macrophage-associated molecules after brain death in islets. *Cell Transplant*. 2003;12(1):27–32.
25. Carlessi R, Lemos NE, Dias AL, Oliveira FS, Brondani LA, Canani LH, Bauer AC, Leitao CB, Crispim D. Exendin-4 protects rat islets against loss of viability and function induced by brain death. *Mol Cell Endocrinol*. 2015;412:239–250.
26. Shinichiro O, Kuroki T, Adachi T, Kosaka T, Okamoto T, Tanaka T, Tajima Y, Kanematsu T, Eguchi S. The effect of selective neutrophil elastase inhibitor on pancreatic islet yields and functions in rat with hypercytokinemia. *Ann Transplant*. 2011;16(4):99–106.
27. Danobeitia JS, Hanson MS, Chlebeck P, Park E, Sperger JM, Schwarzau A, Fernandez LA. Donor pretreatment with IL-1 receptor antagonist attenuates inflammation and improves functional potency in islets from brain-dead nonhuman primates. *Cell Transplant*. 2015;24(9):1863–1877.
28. Johansson U, Olsson A, Gabrielsson S, Nilsson B, Korsgren O. Inflammatory mediators expressed in human islets of langerhans: implications for islet transplantation. *Biochem Biophys Res Commun*. 2003;308(3):474–479.
29. Ehrnfelt C, Kumagai-Braesch M, Uzunel M, Holgersson J. Adult porcine islets produce MCP-1 and recruit human monocytes *in vitro*. *Xenotransplantation*. 2004;11(2):184–194.
30. Jin SM, Shim W, Oh BJ, Oh SH, Yu SJ, Choi JM, Park HJ, Park JB, Kim JH. Anakinra protects against serum deprivation-induced inflammation and functional derangement in islets isolated from nonhuman primates. *Am J Transplant*. 2017;17(2):365–376.
31. Sahraoui A, Kloster-Jensen K, Ueland T, Korsgren O, Foss A, Scholz H. Anakinra and tocilizumab enhance survival and function of human islets during culture: implications for clinical islet transplantation. *Cell Transplant*. 2014;23(10):1199–1211.
32. Dinarello CA. Immunological and inflammatory functions of the interleukin-1 family. *Annu Rev Immunol*. 2009;27:519–550.
33. Delaune V, Berney T, Lacotte S, Toso C. Intraportal islet transplantation: the impact of the liver microenvironment. *Transpl Int*. 2017;30(3):227–238.
34. Weaver JD, Headen DM, Aquart J, Johnson CT, Shea LD, Shirwan H, Garcia AJ. Vasculogenic hydrogel enhances islet survival, engraftment, and function in leading extrahepatic sites. *Sci Adv*. 2017;3(6):e1700184.
35. Montolio M, Biarnes M, Tellez N, Escoriza J, Soler J, Montanya E. Interleukin-1beta and inducible form of nitric oxide synthase expression in early syngeneic islet transplantation. *J Endocrinol*. 2007;192(1):169–177.
36. Cardozo AK, Ortis F, Stirling J, Feng YM, Rasschaert J, Tonnesen M, Van Eylen F, Mandrup-Poulsen T, Herchuelz A, Eizirik DL. Cytokines downregulate the sarcoendoplasmic reticulum pump Ca²⁺ ATPase 2b and deplete endoplasmic reticulum Ca²⁺, leading to induction of endoplasmic reticulum stress in pancreatic beta-cells. *Diabetes*. 2005;54(2):452–461.
37. Yamamoto H, Sugitani A, Kitada H, Arima T, Nishiyama K, Motoyama K, Shiiba M, Kawano R, Morisaki T, Nakafusa Y, Tanaka M. Effect of FR167653 on pancreatic ischemia-reperfusion injury in dogs. *Surgery*. 2001;129(3):309–317.
38. Berchtold LA, Prause M, Stirling J, Mandrup-Poulsen T. Cytokines and pancreatic beta-cell apoptosis. *Adv Clin Chem*. 2016;75:99–158.
39. Amior L, Srivastava R, Nano R, Bertuzzi F, Melloul D. The role of Cox-2 and prostaglandin E2 receptor EP3 in pancreatic beta-cell death. *FASEB J*. 2019;33(4):4975–4986.
40. Nijhoff MF, de Koning EJP. Artificial pancreas or novel beta-cell replacement therapies: a race for optimal glycemic control? *Curr Diab Rep*. 2018;18(11):110.

41. Chang R, Faleo G, Russ HA, Parent AV, Elledge SK, Bernards DA, Allen JL, Villanueva K, Hebrok M, Tang Q, Desai TA. Nanoporous immunoprotective device for stem-cell-derived beta-cell replacement therapy. *ACS Nano*. 2017;11(8):7747–7757.
42. Tamayo T, Rosenbauer J, Wild SH, Spijkerman AM, Baan C, Forouhi NG, Herder C, Rathmann W. diabetes in Europe: an update. *Diabetes Res Clin Pract*. 2014;103(2):206–217.
43. Mooranian A, Tackechi R, Jamieson E, Morahan G, Al-Salami H. Innovative microcapsules for pancreatic beta-cells harvested from mature double-transgenic mice: cell imaging, viability, induced glucose-stimulated insulin measurements and proinflammatory cytokines analysis. *Pharm Res*. 2017;34(6):1217–1223.
44. Cieslak M, Wojtczak A, Cieslak M. Role of pro-inflammatory cytokines of pancreatic islets and prospects of elaboration of new methods for the diabetes treatment. *Acta Biochim Pol*. 2015;62(1):15–21.
45. Eizirik DL, Mandrup-Poulsen T. A choice of death—the signal-transduction of immune-mediated beta-cell apoptosis. *Diabetologia*. 2001;44(12):2115–2133.
46. Cnop M, Welsh N, Jonas JC, Jorns A, Lenzen S, Eizirik DL. Mechanisms of pancreatic beta-cell death in type 1 and type 2 diabetes: many differences, few similarities. *Diabetes*. 2005;54(Suppl 2):S97–S107.
47. Ortis F, Miani M, Colli ML, Cunha DA, Gurzov EN, Allagnat F, Chariot A, Eizirik DL. Differential usage of NF-kappaB activating signals by IL-1beta and TNF-alpha in pancreatic beta cells. *FEBS Lett*. 2012;586(7):984–989.
48. Wang Y, Zhu Y, Gao L, Yin H, Xie Z, Wang D, Zhu Z, Han X. Formononetin attenuates IL-1beta-induced apoptosis and NF-kappaB activation in INS-1 cells. *Molecules*. 2012;17(9):10052–10064.
49. Rojas J, Bermudez V, Palmar J, Martinez MS, Olivar LC, Nava M, Tomey D, Rojas M, Salazar J, Garicano C, Velasco M. Pancreatic beta cell death: novel potential mechanisms in diabetes therapy. *J Diabetes Res*. 2018;2018:9601801.
50. Tan Q, Huang Q, Ma YL, Mao K, Yang G, Luo P, Ma G, Mei P, Jin Y. Potential roles of IL-1 subfamily members in glycolysis in disease. *Cytokine Growth Factor Rev*. 2018;44:18–27.
51. Ding L, Han L, Dube J, Billadeau DD. WASH regulates glucose homeostasis by facilitating glut2 receptor recycling in pancreatic beta-cells. *Diabetes*. 2019;68(2):377–386.
52. Maedler K, Dharmadhikari G, Schumann DM, Storling J. Interleukin-1 beta targeted therapy for type 2 diabetes. *Expert Opin Biol Ther*. 2009;9(9):1177–1188.
53. Tellez N, Montolio M, Estil-les E, Escoriza J, Soler J, Montanya E. Adenoviral overproduction of interleukin-1 receptor antagonist increases beta cell replication and mass in syngeneically transplanted islets, and improves metabolic outcome. *Diabetologia*. 2007;50(3):602–611.
54. Xie Z, Huang G, Wang Z, Luo S, Zheng P, Zhou Z. Epigenetic regulation of Toll-like receptors and its roles in type 1 diabetes. *J Mol Med (Berl)*. 2018;96(8):741–751.
55. Paredes-Juarez GA, Sahasrabudhe NM, Tjoelker RS, de Haan BJ, Engelse MA, de Koning EJP, Faas MM, de Vos P. DAMP production by human islets under low oxygen and nutrients in the presence or absence of an immunoisolating-capsule and necrostatin-1. *Sci Rep*. 2015;5:14623.
56. Westwell-Roper C, Nackiewicz D, Dan M, Ehses JA. Toll-like receptors and NLRP3 as central regulators of pancreatic islet inflammation in type 2 diabetes. *Immunol Cell Biol*. 2014;92(4):314–323.
57. Needell JC, Zipris D. Targeting innate immunity for type 1 diabetes prevention. *Curr Diab Rep*. 2017;17(11):113.
58. Wada J, Makino H. Innate immunity in diabetes and diabetic nephropathy. *Nat Rev Nephrol*. 2016;12(1):13–26.
59. Lu L, Zhou H, Ni M, Wang X, Busuttill R, Kupiec-Weglinski J, Zhai Y. Innate immune regulations and liver ischemia-reperfusion injury. *Transplantation*. 2016;100(12):2601–2610.
60. Wen L, Peng J, Li Z, Wong FS. The effect of innate immunity on autoimmune diabetes and the expression of Toll-like receptors on pancreatic islets. *J Immunol*. 2004;172(5):3173–3180.
61. Lee SM, Choi SE, Lee JH, Lee JJ, Jung IR, Lee SJ, Lee KW, Kang Y. Involvement of the TLR4 (Toll-like receptor4) signaling pathway in palmitate-induced INS-1 beta cell death. *Mol Cell Biochem*. 2011;354(1-2):207–217.
62. Kiely A, Robinson A, McClenaghan NH, Flatt PR, Newsholme P. Toll-like receptor agonist induced changes in clonal rat BRIN-BD11 beta-cell insulin secretion and signal transduction. *J Endocrinol*. 2009;202(3):365–373.
63. Gao Q, Ma LL, Gao X, Yan W, Williams P, Yin DP. TLR4 mediates early graft failure after intraportal islet transplantation. *Am J Transplant*. 2010;10(7):158–1596.
64. Ro H, Hong J, Kim BS, Lee EW, Kim MG, Han KH, Yeom HJ, Lee EM, Jeong JC, Oh KH, Ahn C, et al. Roles of toll-like receptors in allogeneic islet transplantation. *Transplantation*. 2012;94(10):1005–1012.
65. Kruger B, Yin N, Zhang N, Yadav A, Coward W, Lal G, Zang W, SH P, Bromberg JS, Murphy B, Schroppe B. Islet-expressed TLR2 and TLR4 sense injury and mediate early graft failure after transplantation. *Eur J Immunol*. 2010;40(10):2914–2924.
66. Zhang N, Kruger B, Lal G, Luan Y, Yadav A, Zang W, Grimm M, Waaga-Gasser AM, Murphy B, Bromberg JS, Schroppe B. Inhibition of TLR4 signaling prolongs treg-dependent murine islet allograft survival. *Immunol Lett*. 2010;127(2):119–125.
67. Rocuts F, Ma Y, Zhang X, Gao W, Yue Y, Vartanian T, Wang H. Carbon monoxide suppresses membrane expression of TLR4 via myeloid differentiation factor-2 in betaTC3 cells. *J Immunol*. 2010;185(4):2134–2139.
68. Ro H, Lee EW, Hong JH, Han KH, Yeom HJ, Kim HJ, Kim MG, Jung HS, Oh KH, Park KS, Ahn C, et al. Roles of islet toll-like receptors in pig to mouse islet xenotransplantation. *Cell Transplant*. 2013;22(9):1709–1722.
69. Yi S, Wang Y, Chandra AP, O'Hara JM, Wu J, Ouyang L, Burgess JS, Hawthorne W, Wu H, Chadban SJ, O'Connell PJ. Requirement of myd88 for macrophage-mediated islet xenograft rejection after adoptive transfer. *Transplantation*. 2007;83(5):615–623.
70. Schmidt P, Krook H, Goto M, Korsgren O. MyD88-dependent toll-like receptor signalling is not a requirement for fetal islet

- xenograft rejection in mice. *Xenotransplantation*. 2004;11(4):347–352.
71. Hutton MJ, Westwell-Roper C, Soukhatcheva G, Plesner A, Dutz JP, Verchere CB. Islet allograft rejection is independent of toll-like receptor signaling in mice. *Transplantation*. 2009;88(9):1075–1080.
72. Kelley N, Jeltema D, Duan Y, He V. The NLRP3 inflammasome: an overview of mechanisms of activation and regulation. *Int J Mol Sci*. 2019;20(13):3328.
73. Yang Y, Wang H, Kouadir M, Song H, Shi F. Recent advances in the mechanisms of NLRP3 inflammasome activation and its inhibitors. *Cell Death Dis*. 2019;10(2):128.
74. Abderrazak A, El Hadri K, Bosc E, Blondeau B, Slimane MN, Buchele B, Simmet T, Couchie D, Rouis M. Inhibition of the inflammasome NLRP3 by arglabin attenuates inflammation, protects pancreatic beta-cells from apoptosis, and prevents type 2 diabetes mellitus development in apoe2ki mice on a chronic high-fat diet. *J Pharmacol Exp Ther*. 2016;357(3):487–494.
75. Lee HM, Kim JJ, Kim HJ, Shong M, Ku BJ, Jo EK. Upregulated NLRP3 inflammasome activation in patients with type 2 diabetes. *Diabetes*. 2013;62(1):194–204.
76. Jourdan T, Godlewski G, Cinar R, Bertola A, Szanda G, Liu J, Tam J, Han T, Mukhopadhyay B, Skarulis MC, Ju C, et al. Activation of the Nlrp3 inflammasome in infiltrating macrophages by endocannabinoids mediates beta cell loss in type 2 diabetes. *Nat Med*. 2013;19(9):1132–1140.
77. Dong H, Zhang Y, Song L, Kim DS, Wu H, Yang L, Li S, Morgan KA, Adams DB, Wang H. Cell-permeable peptide blocks tlr4 signaling and improves islet allograft survival. *Cell Transplant*. 2016;25(7):1319–1329.
78. Chen C, Ma X, Yang C, Nie W, Zhang J, Li H, Rong P, Yi S, Wang W. Hypoxia potentiates LPS-induced inflammatory response and increases cell death by promoting NLRP3 inflammasome activation in pancreatic beta cells. *Biochem Biophys Res Commun*. 2018;495(4):2512–2518.
79. Lebreton F, Berishvili E, Parnaud G, Rouget C, Bosco D, Berney T, Lavallard V. NLRP3 inflammasome is expressed and regulated in human islets. *Cell Death Dis*. 2018;9(7):726.
80. Tan Y, Nie W, Chen C, He X, Xu Y, Ma X, Zhang J, Tan M, Rong P, Wang W. Mesenchymal stem cells alleviate hypoxia-induced oxidative stress and enhance the pro-survival pathways in porcine islets. *Exp Biol Med (Maywood)*. 2019;244(9):781–788.
81. Sokolova M, Sahraoui A, Hoyem M, Ogaard J, Lien E, Aukrust P, Yndestad A, Ranheim T, Scholz H. NLRP3 inflammasome mediates oxidative stress-induced pancreatic islet dysfunction. *Am J Physiol Endocrinol Metab*. 2018;315(5):E912–E923.
82. Ghiasi SM, Dahllof MS, Osmay Y, Osmay M, Jakobsen KK, Aivazidis A, Tyrberg B, Perruzza L, Prause MCB, Christensen DP, Fog-Tonnesen M, et al. Regulation of the beta-cell inflammasome and contribution to stress-induced cellular dysfunction and apoptosis. *Mol Cell Endocrinol*. 2018;478:106–114.
83. Westermark GT, Davalli AM, Secchi A, Folli F, Kin T, Toso C, Shapiro AM, Korsgren O, Tufveson G, Andersson A, Westermark P. Further evidence for amyloid deposition in clinical pancreatic islet grafts. *Transplantation*. 2012;93(2):219–223.
84. Courtade JA, Klimek-Abercrombie AM, Chen YC, Patel N, Lu PYT, Speake C, Orban PC, Najafian B, Meneilly G, Greenbaum CJ, Warnock GL, et al. Measurement of Pro-islet amyloid polypeptide (1-48) in diabetes and islet transplants. *J Clin Endocrinol Metab*. 2017;102(7):2595–2603.
85. Leon Fradejas M, Kandil D, Papadimitriou JC, del Pino Florez Rial M, Prieto Sanchez V, Drachenberg CB. Islet Amyloid in whole pancreas transplants for type 1 diabetes mellitus (DM): possible role of type 2 DM for graft failure. *Am J Transplant*. 2015;15(9):2495–2500.
86. Denroche HC, Verchere CB. IAPP and type 1 diabetes: implications for immunity, metabolism and islet transplants. *J Mol Endocrinol*. 2018;60(2):R57–R75.
87. Masters SL, Dunne A, Subramanian SL, Hull RL, Tannahill GM, Sharp FA, Becker C, Franchi L, Yoshihara E, Chen Z, Mullooly N, et al. Activation of the NLRP3 inflammasome by islet amyloid polypeptide provides a mechanism for enhanced IL-1beta in type 2 diabetes. *Nat Immunol*. 2010;11(10):897–904.
88. Huang H, Chen HW, Evankovich J, Yan W, Rosborough BR, Nace GW, Ding Q, Loughran P, Beer-Stolz D, Billiar TR, Esmon CT, et al. Histones activate the NLRP3 inflammasome in Kupffer cells during sterile inflammatory liver injury. *J Immunol*. 2013;191(5):2665–2679.
89. Dinarello CA. Interleukin-1 in the pathogenesis and treatment of inflammatory diseases. *Blood*. 2011;117(14):3720–3732.
90. Bersudsky M, Luski L, Fishman D, White RM, Ziv-Sokolovskaya N, Dotan S, Rider P, Kaplanov I, Aychek T, Dinarello CA, Apte RN, et al. Non-redundant properties of IL-1alpha and IL-1beta during acute colon inflammation in mice. *Gut*. 2014;63(4):598–609.
91. Palomo J, Dietrich D, Martin P, Palmer G, Gabay C. The interleukin (IL)-1 cytokine family—balance between agonists and antagonists in inflammatory diseases. *Cytokine*. 2015;76(1):25–37.
92. Larsen CM, Faulenbach M, Vaag A, Ehlers JA, Donath MY, Mandrup-Poulsen T. Sustained effects of interleukin-1 receptor antagonist treatment in type 2 diabetes. *Diabetes Care*. 2009;32(9):1663–1668.
93. Noe A, Howard C, Thuren T, Taylor A, Skerjanec A. Pharmacokinetic and pharmacodynamic characteristics of single-dose Canakinumab in patients with type 2 diabetes mellitus. *Clin Ther*. 2014;36(11):1625–1637.
94. Zhao H, Huang H, Alam A, Chen Q, Suen KC, Cui J, Sun Q, Ologunde R, Zhang W, Lian Q, Ma D. VEGF mitigates histone-induced pyroptosis in the remote liver injury associated with renal allograft ischemia-reperfusion injury in rats. *Am J Transplant*. 2018;18(8):1890–1903.
95. Rydgren T, Oster E, Sandberg M, Sandler S. Administration of IL-1 trap prolongs survival of transplanted pancreatic islets to type 1 diabetic NOD mice. *Cytokine*. 2013;63(2):123–129.
96. Schwarznau A, Hanson MS, Sperger JM, Schram BR, Danobeitia JS, Greenwood KK, Vijayan A, Fernandez LA. IL-1beta receptor blockade protects islets against pro-inflammatory cytokine induced necrosis and apoptosis. *J Cell Physiol*. 2009;220(2):341–347.

97. Matsumoto S, Takita M, Chaussabel D, Noguchi H, Shimoda M, Sugimoto K, Itoh T, Chujo D, SoRelle J, Onaca N, Naziruddin B, et al. Improving efficacy of clinical islet transplantation with iodixanol-based islet purification, thymoglobulin induction, and blockage of IL-1beta and TNF-alpha. *Cell Transplant*. 2011;20(10):1641–1647.
98. McCall M, Pawlick R, Kin T, Shapiro AM. Anakinra potentiates the protective effects of etanercept in transplantation of marginal mass human islets in immunodeficient mice. *Am J Transplant*. 2012;12(2):322–329.
99. Abecassis A, Schuster R, Shahaf G, Ozeri E, Green R, Ochaon DE, Rider P, Lewis EC. alpha1-antitrypsin increases interleukin-1 receptor antagonist production during pancreatic islet graft transplantation. *Cell Mol Immunol*. 2014;11(4):377–386.
100. Wu H, Lu W, Mahato RI. Mesenchymal stem cells as a gene delivery vehicle for successful islet transplantation. *Pharm Res*. 2011;28(9):2098–2109.
101. Ji AT, Chang YC, Fu YJ, Lee OK, Ho JH. Niche-dependent regulations of metabolic balance in high-fat diet-induced diabetic mice by mesenchymal stromal cells. *Diabetes*. 2015;64(3):926–936.
102. Drage M, Zacccone P, Phillips JM, Nicoletti F, Dawson J, Andrew Bradley J, Cooke A. Nondepleting anti-CD4 and soluble interleukin-1 receptor prevent autoimmune destruction of syngeneic islet grafts in diabetic NOD mice. *Transplantation*. 2002;74(5):611–619.
103. Giovannoni L, Muller YD, Lacotte S, Parnaud G, Borot S, Meier RP, Lavallard V, Bedat B, Toso C, Daubeuf B, Elson G, et al. Enhancement of islet engraftment and achievement of long-term islet allograft survival by Toll-like receptor 4 blockade. *Transplantation*. 2015;99(1):29–35.
104. Chang CA, Murphy K, Kane RR, Lawrence MC, Naziruddin B. Early TLR4 blockade attenuates sterile inflammation-mediated stress in islets during isolation and promotes successful transplant outcomes. *Transplantation*. 2018;102(9):1505–1513.
105. Chang CA, Akinbobuyi B, Quintana JM, Yoshimatsu G, Naziruddin B, Kane RR. Ex-vivo generation of drug-eluting islets improves transplant outcomes by inhibiting TLR4-Mediated NFkB upregulation. *Biomaterials*. 2018;159:13–24.
106. Tripathi D, Venkatasubramanian S, Cheekatla SS, Paidipally P, Welch E, Tvinnereim AR, Vankayalapati R. A TLR9 agonist promotes IL-22-dependent pancreatic islet allograft survival in type 1 diabetic mice. *Nat Commun*. 2016;7:13896.
107. Nie W, Ma X, Yang C, Chen Z, Rong P, Wu M, Jiang J, Tan M, Yi S, Wang W. Human mesenchymal-stem-cells-derived exosomes are important in enhancing porcine islet resistance to hypoxia. *Xenotransplantation*. 2018;25(5):e12405