HHS Public Access

Author manuscript

Acta Biomater. Author manuscript; available in PMC 2022 October 01.

Published in final edited form as:

Acta Biomater. 2021 October 01; 133: 87–101. doi:10.1016/j.actbio.2021.05.039.

Designing Biomaterials for the Modulation of Allogeneic and Autoimmune Responses to Cellular Implants in Type 1 Diabetes

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Abstract

The effective suppression of adaptive immune responses is essential for the success of allogeneic cell therapies. In islet transplantation for Type 1 Diabetes, pre-existing autoimmunity provides an additional hurdle, as memory autoimmune T cells mediate both an autoantigen-specific attack on the donor beta cells and an alloantigen-specific attack on the donor graft cells. Immunosuppressive agents used for islet transplantation are generally successful in suppressing alloimmune responses, but dramatically hinder the widespread adoption of this therapeutic approach and fail to control memory T cell populations, which leaves the graft vulnerable to destruction. In this review, we highlight the capacity of biomaterials to provide local and nuanced instruction to suppress or alter immune pathways activated in response to an allogeneic islet transplant. Biomaterial immunoisolation is a common approach employed to block direct antigen recognition and downstream cell-mediated graft destruction; however, immunoisolation alone still permits shed donor antigens to escape into the host environment, resulting in indirect antigen recognition, immune cell activation, and the creation of a toxic graft site. Designing materials to decrease antigen escape, improve cell viability, and increase material compatibility are all approaches that can decrease the local release of antigen and danger signals into the implant microenvironment. Implant materials can be further enhanced through the local delivery of anti-inflammatory, suppressive, chemotactic, and/or tolerogenic agents, which serve to control both the innate and adaptive immune responses to the implant with a benefit of reduced systemic effects. Lessons learned from understanding how to manipulate allogeneic and autogenic immune responses to pancreatic islets can also be applied to other cell therapies to improve their efficacy and duration.

Keywords

allograft; autoimmunity; islet transplantation; immunomodulation; drug delivery; encapsulation

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1. Introduction

1.1. Type 1 Diabetes

Type 1 Diabetes (T1D) is an autoimmune disease caused by aberrant, but targeted, T-cell mediated destruction of insulin-producing beta cells in the pancreas [1]. The resulting loss of blood glucose regulation is associated with increased risks of vascular and neuropathic comorbidities [2]. Despite the fact that T1D is one of the most studied organ-specific autoimmune diseases, the various strategies aimed at intervention, prevention, or reversal of this disease have failed to match animal model predictions of success [3, 4]. Moreover, the global incidence of T1D has increased by 3–4% in the past thirty years, while the factors precipitating this rise remain uncertain [2, 5].

The field of biomedical engineering has made great strides in glucose sensor technologies, making exogenous insulin therapy easier for patients by creating minimally invasive closed-loop systems [6]. However, an artificial pancreas approach, comprised of glucose sensors, control algorithms, and insulin infusion devices, cannot provide physiologic blood glucose control due to delays in glucose sensing from interstitial fluid and insulin action in peripheral tissues [7].

1.2. Clinical Islet Transplantation (CIT)

The clinical transplantation of pancreatic islets of Langerhans has the potential to provide a curative therapy where full physiological glucose-responsive insulin control is restored [8, 9]. Clinical islet transplantation involves the procurement of the allogeneic cadaveric donor organ, mechanical disruption and enzymatic digestion of the pancreas, short-term culture of the resulting islet spheroids, and the infusion of the allogeneic pancreatic islets into the portal vein [10]. The donor islets travel within the bloodstream of the recipient's liver until they become lodged in the microcapillaries, resulting in loss of blood perfusion in the liver tissue distal to the islet [11]. Based on the most recent clinical trial results, most patients (71.6%) receive multiple distinct islet infusions ($n \geq 2$), with some receiving up to six separate islet preparations. It is also important to note that 12.5% of these infusions were procured from multiple pancreatic donors (2–3), meaning islets were pooled from different deceased donors in an attempt to deliver a therapeutic cell dose [12].

With the tremendous advances in donor islet procurement, islet culture, and transplantation techniques, this approach has resulted in several positive clinical trials, with substantial improvements in patient quality of life, restoration of glucose hypo-awareness, and enhanced glycemic control [9, 13–15]. However, the long-term outcomes of this cell therapy have been less than satisfactory, with a general precipitous decline of cell transplant mass that results in the majority of the patients requiring exogenous insulin supplementation after one year [16, 17]. The limited duration of this therapy, as well as the limitations in organ procurement and high cell demand, typically restrict this clinical procedure to a subset of patients with hypoglycemia unawareness and frequent severe hypoglycemic events [18]. Post hoc analysis of these extensive CIT trials has identified early innate immune events and potent adaptive immune responses as key contributors to the rapid decline in the transplanted cell function [19].

Following the implantation of islets into the portal vein, cells are in direct contact with blood. This contact results in the instigation of multiple host responses, including the activation of complement and coagulation cascades, collectively termed the non-specific instant blood-mediated inflammatory reaction (IBMIR) [20, 21]. These early events lead to a significant loss of islet mass (up to ~60%) within two weeks post-implantation [22, 23]. Systemic approaches used to regulate IBMIR have shown promise in pre-clinical and clinical studies; however, their use in standard practice remains challenging due to increased risk of bleeding [24]. Downstream of IBMIR, multiple innate and adaptive immune cells respond to the infusion of the foreign islet graft (Figure 1). In addition to the expected immune pathways activated in response to interactions with the allogenic cell source, Type 1 diabetic recipients also experience the re-initiation of autoimmune responses to the transplanted beta cells. These aggressive immune cell reactions must be fully characterized and potently suppressed to retain the efficacy of the foreign islet graft.

1.3. General Pathways of Allorecognition to Transplanted Cells

Alloimmunity describes the reaction of the host's immune system to a genetically disparate donor graft from the same species. To reject the foreign cellular graft, three main stages of immune responses must occur: recognition, clonal expansion and effector cell maturation, and graft destruction. The recognition of transplanted donor cells by the adaptive immune system occurs through two major pathways: direct and indirect antigen presentation (Figure 1) [25–28]. For direct allorecognition, host immune cells recognize alloantigens presented by major histocompatibility complex (MHC) ligands expressed by the donor allogeneic cells [29]. For indirect allorecognition, host immune cells recognize alloantigens processed and presented by host antigen presenting cells (APC) [29]. T cells (both $CD4^+$ and $CD8^+$) and B cells express the key receptors involved in allorecognition, which are the T cell and B cell receptors (TCR and BCR, respectively).

For transplanted organs and tissues, historical dogma has implicated direct antigen presentation as the dominant allorecognition pathway in early graft recognition [28, 29]. This is due to the route of allorecognition, which is more direct than the requirement of antigen processing and presentation in the context of self-MHC by host APCs in indirect recognition. However, recent examination of $CD4^+$ and $CD8^+$ T cell allorecognition and activation events have revealed challenges in clearly delineating direct from indirect, as there is significant interplay [30]. What is known about early adaptive immune cell recognition is that the presence of host professional APC (e.g., dendritic cells (DCs)) elevates acute rejection, likely by promoting both direct and indirect antigen recognition [31]. In addition, host T cell recognition of foreign MHC alloantigens is exceptionally high, with up to 10% of the recipient's T cells recognizing just a single MHC alloantigen [30, 32, 33]. This results in high direct T cell recognition rates following cellular transplantation, with this frequency elevated with each MHC variant. This high recognition rate further facilitates T cell activation, as the co-binding of $CD8^+$ T cells to MHC I and $CD4^+$ T cells to MHC II in close proximity results in co-stimulation of their effector pathways [34, 35]. Given the key role of direct antigen recognition in islet graft rejection and the high propensity of MHC mismatches due to multiple islet infusions, approaches that mask these antigens or suppress co-activation processes would prove to be highly beneficial.

While the indirect pathway may appear arduous and complex, the importance of the indirect pathway in acute and chronic graft rejection has been validated in several animal model studies [28, 36–39]. For example, a murine TCR transgenic system capable of tracking the $CD8^+$ direct, as well as $CD4^+$ direct and indirect pathways, observed a significantly higher expansion and effector cell maturation in the $CD4^+$ indirect T cell population following allograft implantation, compared to either direct T cell populations [36]. Other murine models have also implicated the indirect recognition pathway as a key contributor to islet allograft rejection [40]. As indirect antigen recognition can be easily initiated at or distal to the graft site, immunomodulatory approaches to mitigate indirect antigen recognition are more focused on blocking the co-stimulation of $CD4^+$ T cells.

Although only more recently demonstrated *in vivo*, the semi-direct pathway also provides a possible explanation to some phenomena not easily explained by direct and indirect antigen recognition pathways [31, 41]. The semi-direct pathway occurs when cell membrane components containing intact allogeneic donor MHC-peptide complexes are transferred to host dendritic cells and presented to the host T cells through direct contact with donor cells or through the internalization or attachment of donor exosomes [25, 30, 42]. With host DCs shown to present the intact MHC-peptide complexes from donor cells, the observed phenomenon of epitope linkage between the CD4+ T cells activated in this manner and the CD8+ T cells activated in the direct pathway finally has an explanation [43]. With this new recognition emerging, additional targets for more effective suppression of immune recognition can be identified [44].

Following allorecognition via direct, indirect, and/or semidirect pathways, the key immune cell players involved in the direct destruction of the foreign cells are the $CD8^+$ cytotoxic T lymphocytes (CTLs), which are provided help by the $CD4^+$ T cells (Figure 1) [30]. Growing evidence for the semidirect pathway suggests that this route of antigen presentation extends the period during which the direct $CD8^+$ T cells can receive T cell help, allowing direct cytotoxic T cells to persist longer [30]. The $CD4^+$ T cells, although typically noncytotoxic on their own, also have been shown to mediate the allograft rejection independently, conceivably through the Fas pathway, if activated through the direct route [45, 46].

The allograft immune response is believed to be majorly T cell-dependent, as indicated by the allograft tolerance in transplant studies in animal models with TCR α or β subunit deficiency [44]. However, the involvement of innate immunity should not be overlooked, as recent studies have underscored the role of monocytes and macrophages in the recognition of non-self in the transplantation setting, as well as the establishment of allospecific innate memory [47–49]. Additionally, the cells of the innate immune system contribute to non-specific graft injury and facilitate the B cell-dependent antibody-mediated graft destruction pathway [44, 50]. Animal transplantation studies have shown that antibody production to the epitopes of the direct pathway is dependent on the help of T cells activated by host APCs [51]. Most importantly, only the indirect pathway results in antibody isotype switching in B cells, which is associated with graft antibody-mediated rejection (AMR) [30, 51] (Figure 1). As such, efforts focused on preventing graft rejection should expand to the modulation of APCs and B cells.

1.4. Autoimmunity, a Special Concern for Islet Transplantation

In Type 1 diabetes, smoldering autoimmune responses to the newly transplanted allogeneic beta cells is an additional facet that contributes to graft recognition and rejection. This is due to the presence of memory T cells specific to type 1 diabetes antigens. Memory T cells naturally arise following the activation and resolution of an immune response to a cognate antigen exposure [52]. Following resolution, a small fraction of T cells persists and converts into long-lived memory T cells, which serve to provide future protection in cases of antigen re-exposure [52, 53]. Importantly, memory T cells react to the re-exposure to the cognate antigen more rapidly and robustly than their naïve counterparts [52].

In most clinical islet transplantation cases, the donor and host are not HLA (human leukocyte antigen) matched, however, in the cases of HLA matching, such as identical twin and HLA-identical sibling transplants, the host autoreactive T cells restricted to the shared MHC molecules can contribute to the rejection of the islet allograft via direct recognition pathway [54–56]. In cases with disparate MHC genes, the self-reactive T cells can still mediate the allograft rejection through the indirect antigen recognition pathway. For example, the implantation of islet allografts into autoimmune diabetic NOD mice resulted in the infiltration of autoreactive T cells that exhibited both allo- and auto-reactivity [54]. This finding supports the hypothesis of “heterologous alloimmunity”, which postulates that memory phenotype T cells specific for one cognate antigen presented by self MHC molecule can also facilitate immune reactions against other peptides presented by non-self MHC, conceivably resulting from peptide molecular mimicry [57–59].

Additionally, compared to naïve T cells, memory T cells are less susceptible to standard immunosuppressive regimens [59–63], indicating that islets infused within T1D patients are insufficiently protected. This concept was validated in retrospective analyses of clinical pancreas and simultaneous pancreas-kidney (SPK) transplant recipients [64–67], which observed the selected destruction of the allogeneic beta cells, but not other allogeneic tissues, and the elevation of T1D autoantibodies, in spite of HLA matching and continuous immunosuppression [65, 67–69]. These results indicate that suppressing adaptive immune responses to allogeneic cellular transplants in patients with pre-existing autoimmunity is extremely difficult, as the self-reactive T-cell effector memory populations are, in fact, dual-reactive and mediate allograft rejection [70].

2. CIT Immunosuppression

To prevent the prompt rejection of the islet transplants, diabetic recipients must receive a continuous and systemic cocktail of immunosuppressive drugs. Most anti-rejection regimens for organ transplantation are two-phased: an aggressive depletion of immune cells in the induction phase, which significantly reduces the frequency of acute graft rejection; and continuation of graft protection in the maintenance phase [71, 72]. The use of immunosuppressive drugs for islet transplantation is typically focused on curbing alloimmune responses, with the induction therapeutics administered immediately prior to transplantation and the maintenance phase immunosuppressive agents administered throughout the lifetime of the graft (see Table 1 for summary of drugs used in clinical islet transplant regimens).

Early agents used in the induction phase were interleukin-2 receptor antagonists (IL-2RAs), such as basiliximab and daclizumab, as they offered a rapid control of T cell populations through inhibition of clonal expansion without T cell depletion [73–75]. These agents have mostly been replaced with antibody-based antithymocyte globulin (ATG), teplizumab, and alemtuzumab, which induce robust T cell depletion, as this approach is more effective in preventing acute rejection [59, 76–80]. Studies have shown, however, that antibody-mediated T cell depletion spares effector memory lymphocytes, which contribute to allo- and auto-reactivity in graft rejection [60, 61]. Thus, recent approaches combining T cell depletion with TNFα inhibition via infliximab or etanercept, with or without IL-2 inhibitors, have observed improved duration of efficacy with reduced side effects [81, 82].

Agents used in the maintenance phase for islet transplantation differ from standard organ transplant approaches due to the sensitivity of islets to steroids [83]. The replacement of standard corticosteroids with calcineurin inhibitors (CNIs) and the mechanistic target of rapamycin (mTOR) inhibitor, sirolimus, resulted in a dramatic improvement in the efficacy of islet grafts [14, 15]. CNIs, cyclosporin A and tacrolimus, are effective in the maintenance phase of islet transplantation as they effectively curb both naïve and memory T cell populations [59, 62]; however, this attribute comes at the cost of decreased general immunity for patients [62]. CNIs have also been associated with beta cell toxicity and post-transplant diabetes mellitus (PTDM) in solid-organ transplants [84, 85]. Contrarily, mTOR inhibitors, like sirolimus, suppress naïve T cell activation and clonal expansion while promoting regulatory T cells, which makes it an attractive agent in the quest to induce graft tolerance [86]. Sirolimus, however, has been associated with increased morbidity and islet toxicity [87–89]. Thus, recent protocols have broadly replaced sirolimus with mycophenolate mofetil (MMF), which inhibits T cell proliferation and downregulates the expression of lymphocyte adhesion molecules required for graft infiltration [12, 90]. Another major advantage of MMF is its ability to reduce the need and/or dosage of CNIs [9, 81].

In the quest to reduce the use of both CNIs and mTOR, other immunosuppressive targets have been developed. Belatacept, a fusion protein with an inhibitory action dependent on a T cell’s maturation state, paired with sirolimus, has been shown to prolong islet allograft survival in a non-human primate study and allow for the achievement of insulin independence in 5 patients for over 500 days post transplantation when additionally combined with MMF [91, 92]. As belatacept does not affect memory T cell populations, its suppressive effect is limited in comparison to the CNIs, conceivably rendering belatacept suboptimal in cell therapy for patients with pre-existing autoimmunity [59, 63]. Other approaches have targeted effector memory cells via blocking of adhesion molecules, as these become upregulated on T cells as they mature [59, 93]. This approach, although partially unverified in clinical islet transplantation, includes the use of MMF in the induction phase, as well as blockades of adhesion markers leukocyte function-associated antigen-1 (LFA-1) via efalizumab [92, 94, 95], CD2 via alefacept [96–98], very late antigen-4 (VLA-4) via natalizumab [99], or lymphocyte Peyer’s patch adhesion molecule-1 (LPAM-1) via vedolizumab [100]. Although these therapeutics require further validation of safety and long-term efficacy, they lay the foundation for targeting key immune pathways to allogeneic islet transplantation within autoimmune patients.

While pharmacotherapy approaches are potent, they come with the requirement of lifelong and stringent medication adherence by the patient and the associated high risk of systemic side effects [101–103]. With these elevated risk and compliance needs, islet transplantation will remain relegated to a selected T1D cohort experiencing extreme challenges in glycemic control. As such, translation of systemic to targeted and localized immunosuppression, as well as the incorporation of more immunoregulatory methods, is needed to treat a broader population.

3. Effects of biomaterial approaches on immune pathways in islet transplantation

3.1. Biomaterial Immunoisolation

With direct antigen recognition as a key pathway that initiates adaptive immune responses, approaches that mask the islet cell surface could substantially suppress immune reactivity to the implant (Figure 2). Contrary to solid-organ transplantation, islet clusters permit ease in the incorporation of biomaterial-based approaches. Cellular encapsulation involves masking of the cell surface from the immune system by imparting a physical, semipermeable, polymer barrier [104–106]. The barrier must balance blocking non-specific IBMIR, as well as allo- and auto- direct recognition and rejection, while also allowing the effective exchange of nutrients, oxygen, metabolites, and hormones, such as insulin. To achieve this balance of protection and exchange, the pore size of the encapsulating material must be highly controlled. The most desirable porosity would be one that allows the efficient permeation of glucose (0.18 kDa; 0.4 nm) and insulin (5.8 kDa, 1.35 nm), but prevents immune cell (~8–15μm), immunoglobulin G (150 kDa; 5.9 nm), immunoglobulin A (300–400 kDa), complement C1q (410 kDa), and immunoglobulin M (950 kDa) infiltration [107, 108]. This tight pore range is challenging to impose, except in highly controlled porous membranes [109]. Furthermore, based on experimental evidence, molecular weight and Stokes radius are not the only aspects governing the diffusion of the molecules into the hydrogel [108].

Hydrogels are widely used in cell encapsulation, as their mechanical properties, along with the high hydration degree, mimic soft tissues [110]. They can be synthesized in the micro and macro scale, which typically imposes a volume increase that prevents intrahepatic infusion [111–113]. To limit cytotoxicity, the process of hydrogel gelation must occur at physiological conditions with mild cross-linkers, which lead the field to the frequent use of alginate, agarose, and polyethylene glycol (PEG), as well as chitosan, collagen, and cellulose in cell encapsulation [110, 114–119].

Alginate is the most extensively used and studied microencapsulation material, reaching the stages of non-human primate and clinical trials [111, 114, 120–123]. Although the mechanical properties, pore size, and permeability of the alginate microcapsules cannot be independently altered, the monomer ratios, molecular weight, and utilization of different divalent cations for cross-linking can be utilized to adjust these parameters [124, 125]. Furthermore, the permselectivity of the alginate can be modified by coating the hydrogel with poly-L-lysine (PLL), PEG, and other polycations, resulting in improved immunoisolation in selected animal studies [126–130].

Agarose macrogels and microbeads have also been explored in animal allograft and autoimmune diabetes models, with one study showing protection of islet allografts in nonobese diabetic (NOD) mice for 100+ days [131–133]. The advantages of agarose include its ease of fabrication, temperature-controlled gelation, inert properties, and enhanced *in vivo* stability, when compared to alginate. The immunoisolatory properties of agarose can also be modulated via gel concentration, which allows for some degree of customization [134]. However, agarose exhibits some instability over time in the presence of cells, which limits it durability *in vivo* [135].

An alternative to encapsulating hydrogels sourced from natural materials is poly(ethylene glycol) (PEG). The synthetic and modular nature of PEG results in a high degree of control over permselectivity, cross-linking density, stability, and reactivity [136–138]. Unlike alginate, which swells over time under physiological conditions, PEG withstands osmotic stress [125, 139]. Its chemical structure also allows for relatively easy functionalization with extracellular matrix (ECM) or peptides such as arginylglycylaspartic acid (RGD), rendering it a highly versatile polymer for cell encapsulation [140–143]. Macro- and micro-scale PEG-based hydrogels have been used for islet encapsulation, with promising survival and immunoprotection observed in animal models [144, 145]. Leveraging cross-linking methods and fluidic technology, conformal coatings, on the scale of tens of microns, have also been generated around islet and stem-cell derived beta cell clusters, resulting in promising protection in several diabetic murine models [146, 147]. Further studies are needed, however, to translate a PEG-based hydrogel to larger animal models and to validate the long-term durability of the material.

Another method for masking the cellular surface is via polymer cell grafting, where polymers are bound to the cell or spheroid surface to mask cell surface proteins and antigens. This approach imparts a negligible increase in cell volume, which allows for the preservation of the current clinical transplant site; however, it is challenged by limited control over permeability and the need for highly cytocompatible polymers and cell surface conjugation methods. Long-chain PEG polymers are the most popular material used in this approach, as the terminal ends of the polymer can be easily controlled for selected cell surface ligation and the polymeric properties of PEG are inherently anti-fouling [148–150]. Islet surface modification using PEG has shown significant promise in both rodent and non-human primate diabetic models when combined with a reduced immunosuppressive regimen [112, 148, 151–154]. It is suspected that polymeric cell surface grafting reduces early inflammatory and innate immune responses to the implanted islets through the generation of a zone of hydration on the islet surface by the PEG chain [155]. However, the long-term immunosuppressive effects of PEG grafting remain unclear as the anti-fouling effects are likely short-term and intra-islet host cell infiltration have been observed. In addition to long-chain PEG grafting, other ultrathin layer-by-layer approaches have shown promise in masking the islet surface within theoretically more durable coatings that still provide the benefits of intraportal infusion [156–160].

While highly promising in murine models, the success of biomaterial encapsulation approaches in larger animal models and clinical trials have been limited. Of concern is that the efficacy of immunoisolation devices relies on the semipermeability of encapsulating

materials, which are designed to ideally allow diffusion of nutrients, oxygen, and metabolites, while blocking host cells, antibodies, and complement to protect the graft [108, 114, 121]. Hydrogels with a porosity sufficient to block direct cell contact can effectively block the direct antigen recognition pathway [161]. Additionally, such hydrogels can block the contact-dependent CD8+ T cell-mediated killing resulting from the indirect pathway, which remains unaffected by encapsulation, as the antigens shed by donor cells can still escape the material barrier, become processed, and be presented by the host APCs to the host T cells [161]. Furthermore, the permeability of the barrier typically supports the diffusion of small pro-inflammatory cytokines (e.g., TNF (17–51 kDa), IL-1 (20 kDa), IFNγ (17kDa) released by indirectly activated T cells into the capsule [108]), meaning the cellular graft could still experience cytokine-mediated cell death (Figure 2) [161].

In addition to T cell activation, humoral immune pathways can also play a role, as accelerated graft failure is associated with the presence and elevation of islet autoantibodies pre- and post-transplantation of islet allografts into T1D recipients [69, 162, 163]. Therefore, the biomaterial permeability should be tailored to block antibody-mediated graft destruction [23, 108]. In addition, *in vivo* animal studies show that biomaterial encapsulation is insufficient in preventing the activation of humoral immunity through the indirect pathway, resulting in the generation and accumulation of donor-specific antibodies at the graft site, albeit with mixed results in terms of infiltration through the material [123, 164–167]. While antibodies may be blocked from directly interacting with the cellular graft, the *de novo* generation of alloantibodies has deleterious consequences in supporting other immune responses, as well as in patient sensitization [50].

3.2 Reducing encapsulated-cell death and material immunogenicity

Biomaterials initiate a foreign body reaction (FBR) depending on their chemical composition, shape, size, and geometry [168, 169]. Directly following implantation, the biomaterial surface becomes coated with a range of host proteins, where the biomaterial surface properties modulate the type and conformation of the adsorbed proteins [168, 170]. This process occurs even before the host immune cells have a chance to interact with the biomaterial surface, which means that the innate immune cell adhesion molecules interact with these surface-adsorbed proteins and direct the resultant immune response [168, 171, 172]. Following inflammatory cell infiltration and interaction with the biomaterial surface and adsorbed proteins, monocytes differentiate into macrophages and mediate the wound healing process at the site of implantation [168]. In most cases, the response to the material persists, resulting in a shift toward chronic inflammation, which leads to macrophage fusion, the generation of foreign body giant cells (FBGCs), and granulation tissue formation, leading to eventual foreign body response (FBR) via fibrous capsule formation around the implant [168]. When cells are placed within these biomaterial implants, host responses are further exacerbated, as shed antigens and danger signals released by the cells activate the adaptive immune arm [123, 164]. Globally, these responses detrimentally impact graft efficacy. For example, two recent clinical trials of islet and beta-cell transplants exhibited substantial declines in cellular function as the host responses to the implant transitioned from acute to chronic inflammation, and the FBR fully encapsulated the graft [173, 174].

A primary approach to modulate FBR is via the manipulation of the material properties, such as chemical structure, material charge, surface topography, mechanical properties, and crosslinking features. Improvement of material purity can improve biocompatibility and reduce immunogenicity [175, 176]. In addition, incorporating materials with biocompatible features, such as PEG or zwitterionic hydrogels, has shown decreased FBR to the implanted materials [177–180]. Alternatively, utilizing natural degradation processes of the material and/or modulating the material geometry can direct a more “healing” host cell response to the implant [181–183]. The careful selection and tailoring of material properties and features to minimize foreign body responses to the implant also imparts additional benefits in adaptive immune responses. Specifically, minimizing material immunogenicity can skew the innate APC population towards a more tolerogenic phenotype, which can reduce activation of the adaptive effector cells and potentially improve implant efficacy and/or graft survival [179, 184] (Figure 3).

Beyond responses to the material alone, the cellular cargo contained within the implant also dramatically contributes to the nature of the host response. Thus, minimizing the stress and death of the transplanted cells is crucial for curtailing the immune response to the graft. Intracellular factors, such as damage-associated molecular patterns (DAMPs), are released during cell necrosis due to tissue injury related to the donor organ procurement process [185]. Clinical studies in solid-organ transplants, where living-donor grafts are possible, such as kidney or liver, showed lower levels of immune cell infiltration and cytokine concentrations compared to cadaveric donor grafts [186, 187]. Studies show that both DAMPs and autoantigens, which are released during secondary necrosis, can activate APCs and induce an adaptive immune response, promoting chronic inflammation, fibrosis formation, and eventual graft rejection [188–190]. Thus, in the selection of the implantation site, awareness of vascular accessibility to ensure adequate nutrient delivery should be a critical parameter [191, 192]. While inflammation at the implant site can have deleterious effects for the transplanted cells, certain pro-inflammatory cytokines and immune cells have been shown to be in fact pro-angiogenic [193, 194]. This in turn indicates that low levels of inflammation at the implant site might be beneficial to the long-term survival of transplanted cells by promoting device vascularization. Alternatively, biomaterial and/or cellular approaches that enhance vascular infiltration into the graft site should result in improved cell viability and function [195–197] (Figure 3). For encapsulation devices on the macroscale, ensuring high cellular viability post-implantation is particularly challenging, as their large scale barriers introduce inefficient nutrient delivery [198]. Promoting more efficient accessibility of critical nutrients, particularly oxygen, is a challenge that several groups [199–202], including our own [203], have aimed to resolve. Enhancement of encapsulated beta cell viability has also been pursued through the use of agents acting on the encapsulated cells directly and provides an additional route of curtailing the indirect pathway, where donor cell death plays a critical role in delivering antigens to the host APCs [204–206]. Overall, supporting the viability of encapsulated islets results in two-fold benefits: it reduces the release of immunogenic intracellular contents; and preserves the cell load required for the achievement of glycemic control.

3.3 Designing materials for active and local immunomodulation

In addition to the careful selection of material properties and the implantation site, the biomaterials used for cell transplantation can be further enhanced by leveraging them for controlled drug release. These local drug delivery platforms can act as a sparing factor for systemic immunosuppression, resulting in decreased systemic side effects and enhanced general immune equilibrium, as well as a means to locally deliver novel agents that may not be suitable for systemic delivery. These local agents can target specific or multiple immune pathways that are activated following the implantation of either an unencapsulated or encapsulated cell platform (Figure 4).

The transplantation procedure, as well as cell death within tissue graft, initiates local tissue inflammation, which plays a key instructive role in both innate and adaptive immune responses, such as cell maturation and pro-inflammatory cytokine production [207]. This is further exacerbated in cases of cadaveric organ transplantation, such as clinical islet transplantation, due to a series of inflammatory changes occurring at the time of death of the donor that lead to inferior graft outcomes when compared to living donor transplants [187, 207]. The local delivery of anti-inflammatory agents, cytokines, and antioxidants provide an approach for reducing inflammation and downstream immune activation pathways, while potentially promoting a “healing” microenvironment at the graft site [208–211] (Figure 4.1). However, further studies are required, especially in T1D autoimmune models, to validate the potential efficacy of these approaches.

Utilization of the implant material to locally deliver agents is a classic approach of controlled drug delivery. Novel approaches incorporating immunosuppressive drugs, such as mTOR inhibitors, CNIs, and MMT, for local delivery provide a potential solution to the comorbidity problem associated with the systemic use of these agents [212–215] (Figure 4.2). In a complementary approach, a recent promising study adapted dibenzocyclooctyne (DBCO)-azide click chemistry to create re-fillable alginate drug depots capable of binding freshly injected intravenous functionalized drugs, allowing for long-term localized immunosuppression [212]. A challenge of translating effective systemic agents to local approaches, however, is that the delivery method can impart differences in immune cell effect or impair implant engraftment/survival. For instance, while systemic delivery of fingolimod has been found to reduce islet allograft rejection in animal model studies, its local delivery was detrimental to islet viability and function [216].

Local immunomodulation can also be achieved by looking beyond traditional immunosuppressive agents and instead harnessing the potential of local chemokine delivery to selectively limit the infiltration of effector T cells (Figure 4.3). In addition to impairment of recruitment, selective agents can also preserve or even recruit regulatory T cells to the implant site. For example, the chemokine CXCL12 has been shown to impart such effects on host T cell populations, while delivering survival signals for beta-cells and curbing inflammation [217–219]. Linking this chemokine onto the islet surface showed prolonged allograft survival but did not translate to the autoimmune diabetes mouse model [220]. When CXCL12 was combined with alginate encapsulation, graft efficacy and durability was substantially increased in both standard diabetic allograft and NOD models, when compared to alginate encapsulation alone [220]. In addition, further tests indicated that CXCL12 plus

encapsulation protects grafts from memory T cells. In this study, recipient NOD mice were pretreated with skin transplantation from the donor mice strain, which subsequently rejected, and then received CXCL12-alginate encapsulated allograft islets [220]. Despite the presence of memory T cells created through the allograft skin transplantation and rejection process, the transplanted CXCL12-alginate encapsulated allograft islets survived significantly longer than alginate alone implants [220]. Given that both the CXCL12 and alginate encapsulation approach was needed to impart the desired effect, this approach implicates that the immune pathways blocked by encapsulation are distinct to those impaired by CXCL12.

Another approach to control immune responses seeks to mimic natural inhibitory and/or tolerogenic immune pathways through the modulation of specific immune cell interactions, such as Fas- Fas ligand (FasL) and programmed death ligand (PD-L1) (Figure 4.4). The immune checkpoint receptor Fas is a particularly desirable target, as nearly all cells of the immune system express this receptor and binding initiates activation-induced cell death (AICD), a native pathway crucial for the maintenance of self-tolerance [221]. While the Fas-Fas ligand (FasL) apoptotic pathway has long been implicated in the immunopathogenesis of autoimmune T1D, it is emerging as a target of interest in islet transplantation to trigger apoptosis in target cells after direct cell surface contact [221–224]. Recent approaches had used materials to locally present Fas ligand within the transplant site, where a shift in graft survival of allogeneic islets was observed when the FasL material was present [222–224]. The efficacy of this approach was further elevated when combined with a systemic short course of rapamycin, implicating a synergy between the local and systemic agents.

Cytotoxic T lymphocyte populations are more susceptible to FasL than the regulatory T cell populations, which adds to the attractiveness of this approach in inducing graft tolerance [221]. However, animal studies indicate that primed memory T cells were less susceptible to Fas-mediated AICD when compared to their naïve counterparts, potentially implicating that this approach might not be suitable for CIT in T1D patients where pre-existing autoimmunity results in a large population of memory T cells [54, 70, 225].

Of interest, the matter of delivery and presentation of FasL may be a key modulator of the downstream immune response, as FasL exists in two forms leading to duality in mediating apoptosis: a pro-apoptotic membrane-bound form expressed on the cell surface; and a usually anti-apoptotic soluble form created by proteolysis of the membrane-bound form that can become pro-apoptotic if bound to the surrounding matrix proteins [221, 226, 227]. This polarization of action is important to consider when designing biomaterials aimed at local immunomodulation, as presenting this protein in a soluble, rather than surface grafted, manner could switch downstream pathways from apoptotic to effector [227]. This phenomenon might not be isolated to the function of FasL, thus requiring factoring in the manner of delivery and the kinetics of therapeutic dose release in the design of immunomodulatory biomaterials.

The local presentation of another immune checkpoint, programmed cell death-ligand 1 (PD-L1), has also recently showed improved survival of allogeneic islet allografts in rodent models, when combined with short-course rapamycin treatment [228, 229]. For this approach, two methods were examined: local surface presentation onto the islet itself;

and local surface presentation on a microbead co-transplanted within the islet graft. While the streptavidin (SA) mediated grafting of PD-L1 directly on islet surface supported lasting allograft survival and function in 90% of hosts, the presentation of PD-L1 on the surface of PEG-4MAL hydrogel microspheres resulted in the long-term function of ~58% of allografts [228, 229]. Both approaches yielded increases in local populations of regulatory T cells, implicating the benefits of leveraging this checkpoint in promoting more regulatory phenotypes. While the direct islet grafting approach resulted in improved allograft protection, the off-the-shelf accessibility of the material-only approach may lead to ease in clinical translation. Future studies should examine the efficacy of this approach in autoimmune models.

Overall, the examination of adaptive immune responses to allogeneic islets indicates the need for a combinatory approach that targets multiple activation pathways. For example, combining cellular encapsulation, which blocks the direct recognition pathway, with localized immunomodulatory agents that target both the indirect pathway and memory T cells would result in optimal transplant protection. As local immunomodulation may be imperfect, there are other complementary approaches that may provide further benefits, such as the integration of agents capable of scavenging diffusible pro-inflammatory cytokines before they can impart cellular damage [230]. In addition, a deeper understanding of knowledge gaps in the field regarding the role of indirect allorecognition in the autoimmune setting, and the resulting potential drug targets is needed to provide more targeted immunomodulatory approaches. Recent research in the development of humanized mouse models and benchtop diabetes screening platforms generated using human cells can facilitate the discovery of these key immune pathways [231, 232].

4 Conclusions and Future Recommendations

Beta cell replacement therapy has tremendous potential in providing durable and physiological glycemic control in people with T1D. Restricting its success, however, are the aggressive allogeneic and autoimmune responses following cadaveric islet infusion. While current immunosuppressive regimens are generally successful in curbing allogeneic immune responses, they fail to control the autoreactivity of the host immune system and restrict this therapy to the most at-risk T1D cohort.

The careful and targeted utilization of biomaterial-based approaches has the potential to both improve immunosuppression and decrease systemic impacts. While cellular encapsulation has been an appealing and well investigated approach to block direct antigen recognition and cell-mediated effector immune cell attack, it is evident that it is insufficient in blocking indirect immune activation and its downstream pathways, particularly in large scale models and humans. As such, tailored immunomodulatory biomaterial approaches that provide more instructive cues to the responding immune cells are needed, either to suppress their activation or convert these cells towards a more regulatory phenotype. The inherent modular nature of materials provides a unique platform for customizing immunomodulatory materials that inhibit or suppress specific pathways at the graft site. Thus, future work should continue to leverage materials for not only classic drug release, but also for scavenging activity and delivering instructional cues.

Finally, in order to efficiently optimize immunomodulatory biomaterial device design for cell therapy, more clinically predictive *in vitro* studies are needed to fill the knowledge gaps. Utilizing simplified but robust *in vitro* platforms for testing of biomaterial approaches conceivably allows for reductions in time from bench to bedside, research cost, and use of animals in *in vivo* studies. Lessons learned from understanding how to manipulate the allogeneic and autogenic immune responses to pancreatic islets can be applied to other diseases where underlying autoimmunity stands in the way of potential cell therapy, such as autoimmune thyroiditis (Hashimoto's disease) and autoimmune adrenalitis (Addison's disease) [233–235]

Acknowledgements

The authors are grateful for funding from the US National Institutes of Health grants DK126413 and DK122638, as well as from JDRF grant 3-SRA-2021-1033-S-B. M. M. Samojlik is a predoctoral fellow in the NIH NIDDK T32 Interdisciplinary Graduate Program in Type 1 Diabetes and Biomedical Engineering (DK108736). All figures created with BioRender.com

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Statement of significance

This review explores key immunologic concepts and critical pathways mediating graft rejection in Type 1 Diabetes, which can instruct the future purposeful design of immunomodulatory biomaterials for cell therapy. A summary of immunological pathways initiated following cellular implantation, as well as current systemic immunomodulatory agents used, is provided. We then outline the potential of biomaterials to modulate these responses. The capacity of polymeric encapsulation to block some powerful rejection pathways is covered. We also highlight the role of cellular health and biocompatibility in mitigating immune responses. Finally, we review the use of bioactive materials to proactively modulate local immune responses, focusing on key concepts of anti-inflammatory, suppressive, and tolerogenic agents.

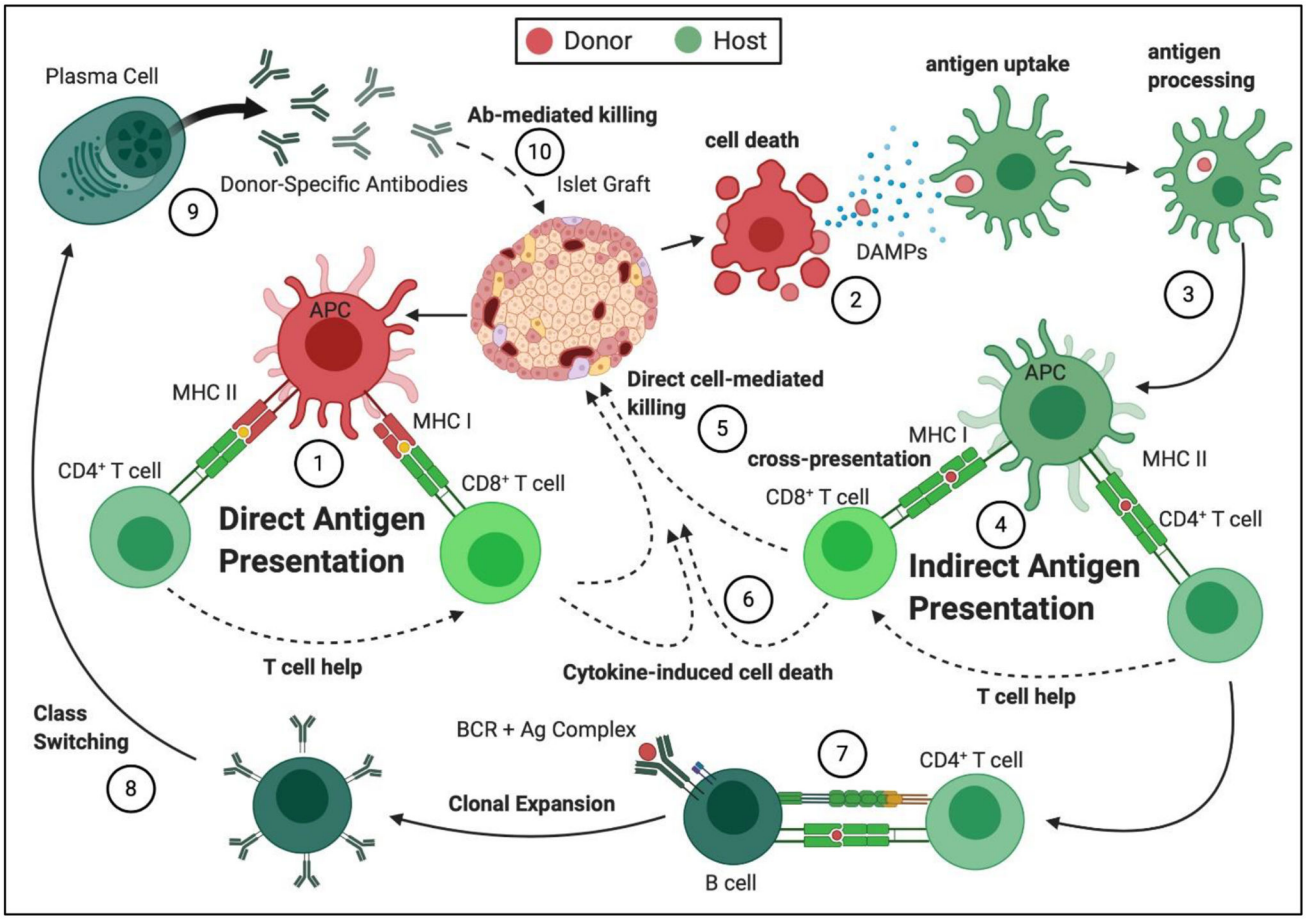

Figure 1: Summary of immune pathways of recognition and rejection following implantation of allogenic pancreatic islets.

(1) Direct antigen presentation: Donor islet antigen presenting cells (APCs) present antigens to the host T lymphocytes through MHC Class I for $CD8^+$ T cells and MHC Class II for $CD4^+$ T cells. $CD4^+$ T cells become activated and provide help to the $CD8^+$ T cells, resulting in their clonal expansion and activation. Auto-antigens can also be recognized in this manner, when donor and host MHC match. **(2)** Donor cell death: Dying transplanted cells shed antigen and release danger-associated molecular patterns (DAMPs). **(3)** Antigen uptake and processing: The presence of DAMPs during antigen uptake and processing by APCs initiate and perpetuate effector signals in APCs (e.g. elevated MHCII expression). **(4)** Indirect Antigen Presentation: Processed host allo- or autoantigens present to host T cells in context of the self-MHC on the host APCs, resulting in T cell clonal expansion and activation. **(5)** Direct Cell-Mediated Killing: Cytotoxic T lymphocytes (CTLs) migrate to the implant site and initiate cell-cell interactions with the donor cells, resulting in destruction of the donor cell graft. **(6)** Cytokine-Induced Cell Death: Activated T cells and innate immune cells produce pro-inflammatory cytokines, which damage cells within the graft site. **(7)** CD4+ T cell- Mediated B cell Activation: $CD4^+$ T cells, activated through the indirect pathway, interact with antigen-specific B cells through CD40-CD40L and provide Signal 2 for B cell activation, initiating their proliferation and differentiation. **(8)** Antibody Class Switching: $CD4^+$ T cells activated through the indirect pathway allow for class switching

of the produced antibodies to isotype IgG, which is associated with antibody-mediated rejection (AMR). **(9)** Release of Donor-Specific Antibodies (DSA): Production of DSAs by plasma cells results in acute and chronic **(10)** Antibody-Mediated Graft Destruction, which involves antibody binding to donor cell surface antigens, complement activation, and graft destruction.

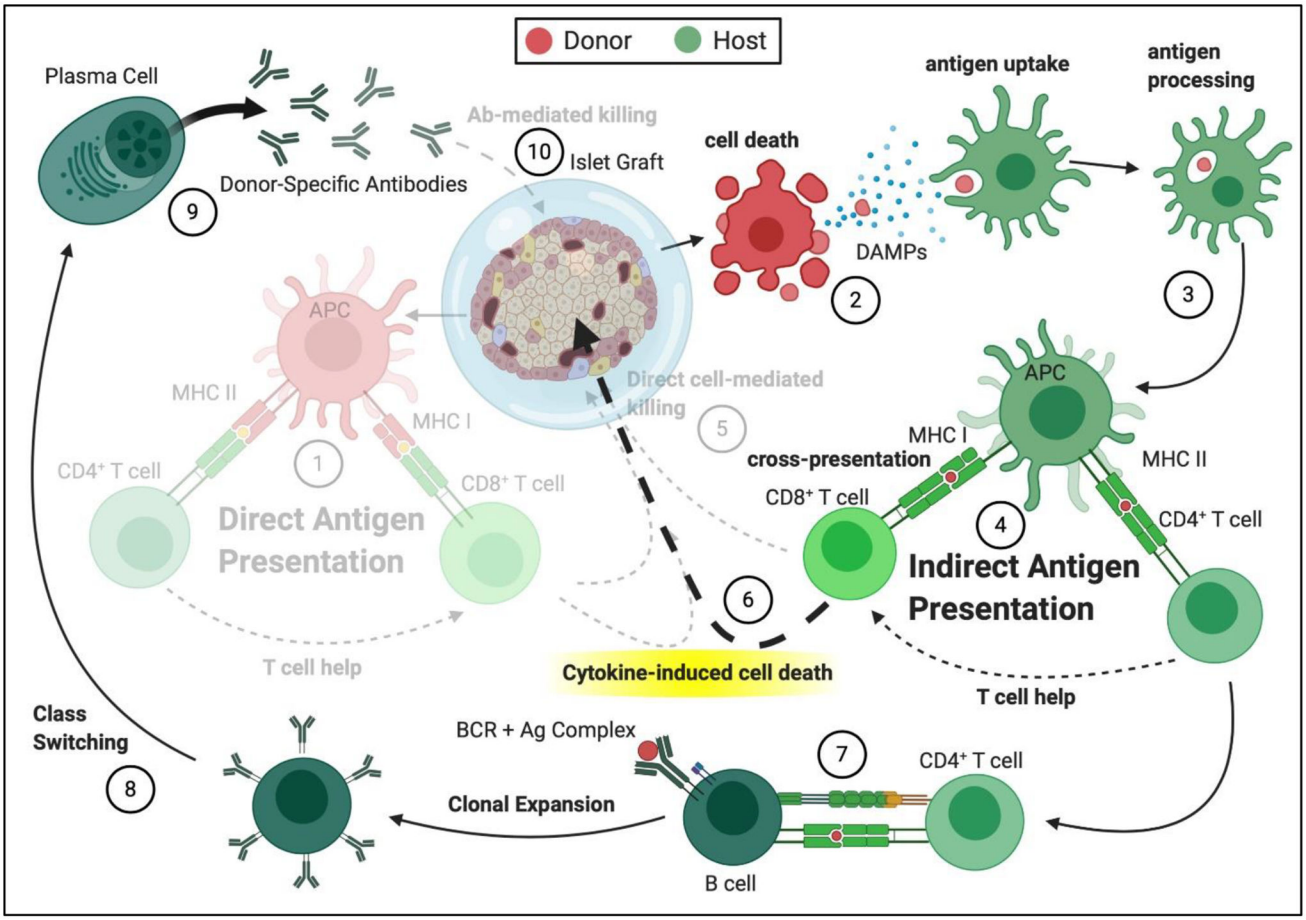

Figure 2. Potential impacts of cell encapsulation on immune pathways in pancreatic islet transplantation

(1) Direct antigen presentation is blocked through use of immunoisolatory biomaterials. **(2)** Donor cell death persists and can be exacerbated due to deficiency in oxygen availability, elevating antigen shedding, which can diffuse through the semipermeable membrane. This supports **(3)** antigen uptake and processing and **(4)** retention of indirect antigen presentation. **(5)** Direct cell-mediated killing is blocked by the immunoisolatory material, which suppresses direct host immune cell infiltration. But, **(6)** cytokine-induced cell death can still occur, as cytokines can permeate the porous biomaterial. **(7)** CD4+ T cell-mediated B cell activation, **(8)** antibody class switching, and **(9)** production of donor-specific antibodies continues uninterrupted, although, **(10)** antibody-mediated graft destruction can be blocked by some encapsulating materials.

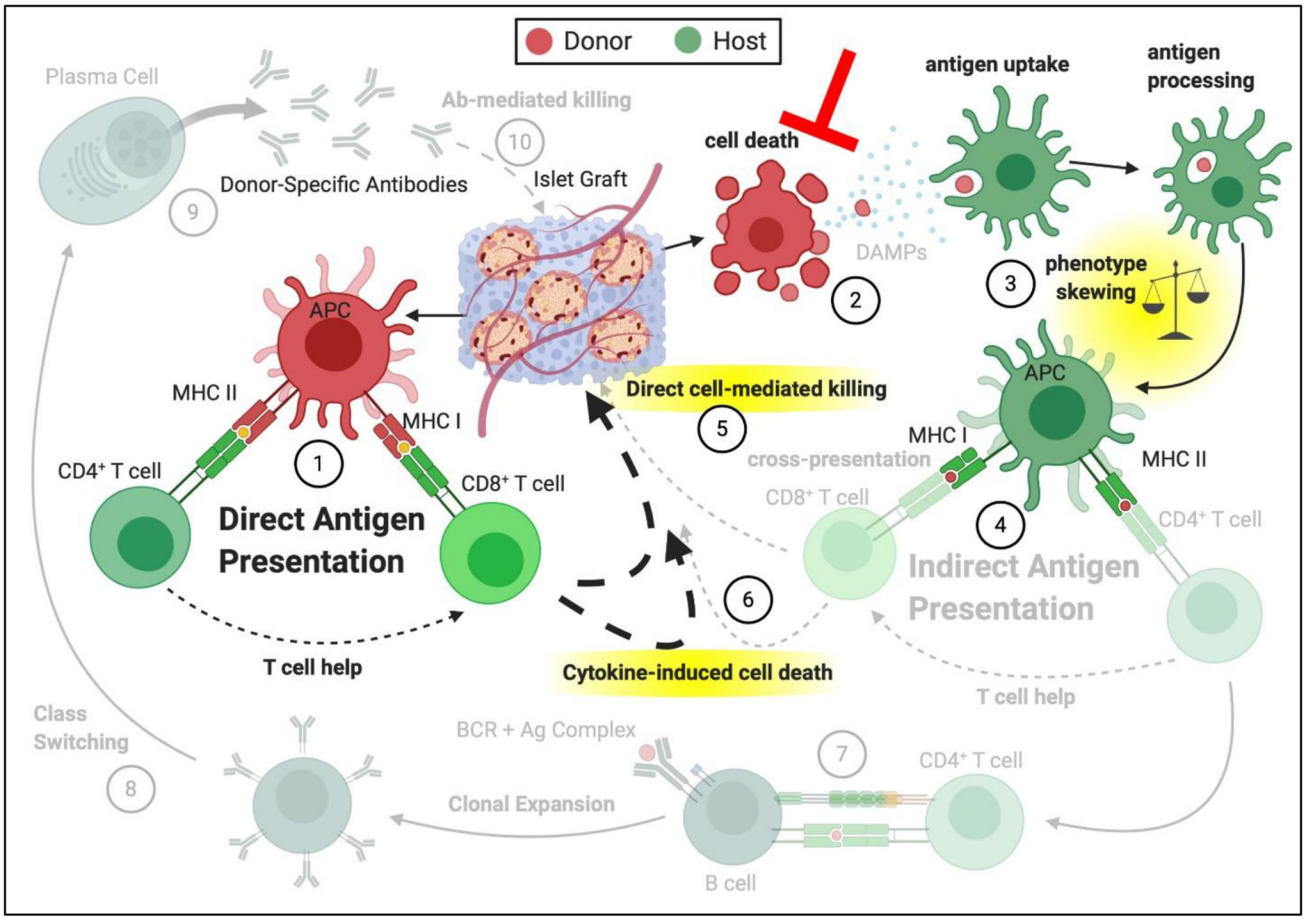

Figure 3. Potential impacts of reduced material immunogenicity and improved cell implant viability on immune pathways in pancreatic islet transplantation

(1) Direct antigen presentation is retained for non-immunoisolatory, vascularized scaffolds. Approaches focused on improving donor cell viability post-transplantation, through vascularization, optimized 3-D material implants, and/or material-driven oxygen supplementation can result in reduced **(2)** donor cell death or change in the cell death pathway, which reduces DAMPs and/or shed antigen. **(3)** Antigen uptake and processing can be modified in the absence of DAMPs, leading to skewing of the phenotype of the innate APCs involved in the **(4)** indirect antigen presentation. APC phenotype shift can alter interactions with T lymphocytes and abrogate their activation. **(5)** Direct cell-mediated killing and the **(6)** cytokine-induced cell death can be mediated through the direct pathway only. Due to decreased T cell activation in the indirect pathway, **(7)** CD4+ T cell-mediated B cell activation, **(8)** antibody class switching, **(9)** production of donor-specific antibodies, and **(10)** antibody-mediated graft destruction can also be minimized.

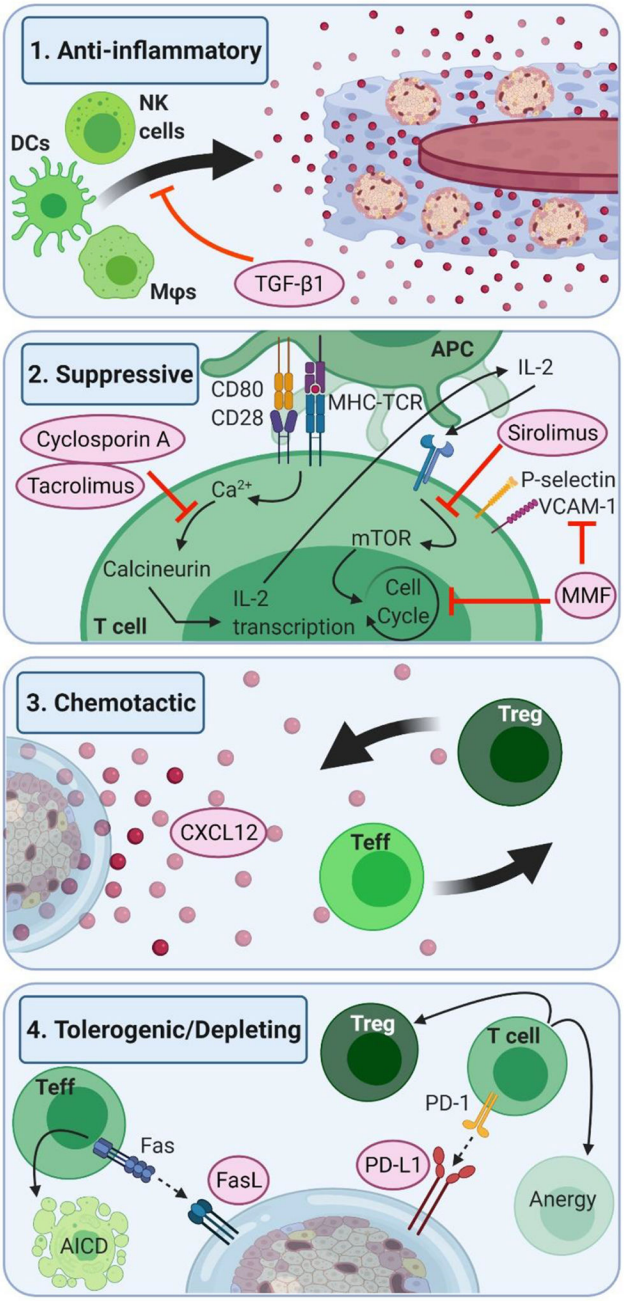

Figure 4. Potential impacts of local immunosuppression and tolerogenic drug delivery on immune pathways in pancreatic islet transplantation

(1) Anti-Inflammatory biomaterial approaches can reduce inflammation in the immediate graft area, through the use of locally delivered anti-inflammatory drugs or cytokines, such as TGF-β1, which results in decreased infiltration of the innate cell populations responsible for aggravating adaptive responses to the graft. **(2)** Suppressive drug approaches utilize the local delivery of known systemic immunosuppressants, such as CNIs, mTOR inhibitors, or MMF which allow for the achievement of local suppression of the effector T cells, with the added benefit of decreased systemic side effects. **(3)** Chemotactic agents used in local delivery aim to stop the infiltration of effector immune cells, resulting in lowered immune response to

the graft, without imparting a systemic lowered response to pathogenic infections. Agents such as CXCL12 have the additional benefit of increasing regulatory T cell infiltration, which aids in promoting graft tolerance. **(4)** Tolerogenic/Depleting strategies, such as local presentation of FasL or PD-L1 on biomaterial surface utilize potent native immune checkpoints and activation-induced cell death (AICD) pathways for the depletion of effector T cells, and induction of regulatory T cells in the graft environment.

Table 1.

Summary of key immunosuppressive drugs for islet transplantation

Immunosuppression Phase	Category	Immunosuppressive Agent	Target	Naïve T cell Effect	Memory T cell Effect	References
Induction	T cell depletion	Alemtuzumab	CD52	depletion	sparing	[61, 62]
		Teplizumab	CD3	depletion	expansion	[81, 80]
		Antithymocyte Globulin	polyclonal	depletion	sparing	[78, 61, 62]
	T cell activation inhibition	Basiliximab	IL-2R	inhibition	sparing	[74, 76]
		Daclizumab	IL-2R	inhibition	sparing	[74, 76]
Maintenance	Antiproliferative	Mycophenolate Mofetil	IMPDH	inhibition	inhibition	[93]
		Sirolimus	mTOR	inhibition	expansion	[97]
	Co-stimulation inhibition	Belatacept	CD28-B7	inhibition	sparing	[64, 97]
	Calcineurin inhibition	Tacrolimus	Calcineurin	inhibition	inhibition	[97, 60]
		Cyclosporine A	Calcineurin	inhibition	inhibition	[97, 60]
	Anti-inflammatory	Glucocorticoid	Glucocorticoid receptor	inhibition	expansion	[86]
		Infliximab	TNF	inhibition	mixed reports	[84]
	Lymphocyte migration inhibition	Alefacept	CD2-LFA-3	sparing	depletion	[102, 97]
		Efalizumab	LFA-1	sparing	depletion	[99, 97]
		Natalizumab *	VLA-4	sparing	inhibition	[60, 103]

* Agent of interest that has not yet been applied for use in CIT

Acta Biomater. Author manuscript; available in PMC 2022 October 01.