

# Islet Transplantation Challenge - Human Islet Longevity: A Potential Solution from Bone Marrow Cells

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## Islet Transplantation: The Problem of Islet Survival

The occurrence of diabetes mellitus has increased steadily worldwide [1]. Improvements in the immunosuppressive regimen have made clinical islet transplantation a feasible choice which to treat type 1 diabetes [2]. However, efforts toward routine islet cell transplantation have been hindered not only by scarce islet availability but also by low rates of post-transplantation islet survival and function [3,4]. The number of islets generally required to achieve insulin independence is 12000 islet equivalents per kg of recipient's body weight, and this number is usually obtained by transplanting more than one islet preparation per patient [5]. Early graft loss resulting from repeated transplantations of islets [6] is a major component of islet primary nonfunctioning, which occurs in syngeneic islet transplantation [7] as well as T-cell activation [8,9]. Large numbers of islets are destroyed, and only a small proportion are successfully engrafted after transplantation [4,10,11]. These findings suggest that poor islet viability—not just allograft rejection and recurrence of autoimmunity—may contribute to early-stage loss of islet function. In experimental models of syngeneic islet transplantation, up to 60% of islet cell mass undergoes apoptosis, and half of this loss occurs within the first 3 days after transplantation [12]. Functional islet mass is reduced even in successfully transplanted recipients compared with healthy people. These failures—the result of islet damage before transplantation—are the major barrier to the widespread use of islet transplantation.

## Factors Contribute to Functional Failure of Isolated Islets

Reduced viability and functional impairment caused by stress during isolation and implantation [13,14] are major reasons for the need to transplant a large number of islets to obtain desired results. Proinflammatory cytokines such as interleukin-1 $\beta$  (IL-1 $\beta$ ), tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), interferon- $\gamma$  (INF- $\gamma$ ), cyclooxygenase-2 (COX-2), and nitric oxide (NO) as well as chemokines secreted from islets play an important role in islet survival *in vitro* and at different stages after transplantation [15]. Recruitment of activated leukocytes toward islets as a result of cytokine and chemokine secretion could cause islet injury and participate in presenting foreign antigens to the macrophages, which leads to acute immune response and death or impairment of  $\beta$  cells. Thus, the amount of cytokines released by donor pancreatic islets is directly related to islet survival after isolation—including the rate at which pancreatic islet tissue undergoes apoptosis *in vitro* [16,17]—and transplantation outcome in the recipient [18]. Blocking apoptosis through the inhibition of cytokines could help protect pancreatic islets from either cell-mediated or non-cell-mediated destruction [19]. Several approaches have been used to examine this hypothesis. Isolated human islets have been shown to secrete TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and nitric oxide. Secretion of these mediators was shown to be augmented by stimulation of the islets with IL-1 $\beta$  [3] and others [20]. IL-1 $\beta$  is considered to be the key initiator of inflammatory response and one of the proinflammatory cytokines that may mediate primary

nonfunction of islets *in vitro* and have the greatest effect on outcome post-transplantation [21].

## Approaches to Ensuring Islet Survival

Numerous efforts have been made to improve islet cytoprotection—that is, to ensure islet survival, function and transplant success [19]. Chemical-based strategies for islet cytoprotection, such as the early application of perfluorocarbons to the organ preservation solution (two-layer method) allows for increased availability of oxygen to the tissue. This step permits increased adenosine triphosphate (ATP) content in the organ [11,22,23]. Use of additives in the culture media (antioxidants, hormones, etc.) may result in reduced islet cell death, improved islet recovery after isolation, and better function, representing a minimally invasive strategy for the optimization of islet engraftment. Molecular biological approaches to achieve islet cytoprotection have used various vectors (including viruses) to transfer genes that may inhibit apoptosis or increase growth factors [24-26]. Delivery of cytoprotective proteins by protein transduction allows delivery of proteins/peptides fused to small cationic cell-penetrating peptides known as protein transduction domains to cells or tissues [27]. However, the goal of maintaining islet viability has not yet been fully achieved by these efforts.

## The Microenvironment of The Pancreas Facilitates Islet Survival and Function

The microenvironment of the pancreas enables islets to be immunized from insults to allogeneic tissue and permits repair of islet injury and regeneration of functional pancreatic endocrine tissue. The finding that pancreatic transplantation has resulted in better insulin independence than islet transplantation alone [28,29] supports the notion that islet injury and microenvironment loss from the isolation process may be the major cause of islet death after transplantation. Another example of microenvironmental effect on islet  $\beta$  function is that Mist1 null mice exhibit small islet size and aberrant islet function even though Mist1 has been identified only through expression in exocrine cells—such as acinar cells—not directly related to islet  $\beta$  cells [30-33]. The absence of Mist1 alters the pancreatic microenvironment, which generates unsuitable circumstances for islet development. The successful use of bone marrow to repair damaged tissues encourages the use of stem cells to create a microenvironment for islet longevity,

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which is further supported by the accumulating evidence based on investigations into the regenerative capacity of stem cell tissue, of stem cells' low immunogenic thresholds and production of homing and trophic factors promoting vasculogenesis.

### Stem Cells and Islet $\beta$ Cell Function

For diabetes therapy, it is not clear whether it will be sufficient to produce only  $\beta$  cells—the islet cells that manufacture insulin—or whether other types of islet cells are also necessary. B cells isolated without other types of islet cells are less responsive to changes in glucose concentration than intact islet clusters made up of all islet cell types. This may be the major reason why different sources of stem cells have been proposed for the production of  $\beta$  cells; in practice, however, fully functional islet cells have not yet been derived from stem cells. Bone marrow-derived stem cells have been considered the best-characterized stem cell source, but current research suggests that these cells do not differentiate into  $\beta$  cells *in vivo*, although they can support pancreatic growth *in vivo* and can be manipulated *in vitro* to differentiate into  $\beta$  cells [34]. However, pure bone marrow sub stem population pretreated by cytokines are able to generate insulin positive cells *in vivo* [35] which Bone marrow-derived stem cells can migrate towards a site of damage and differentiate under the influence of factors from the microenvironment (e.g. cell-cell, cell-extracellular matrix interactions and growth factors) [36].

### Bone Marrow Cells can Regenerate the Pancreatic Microenvironment

Animal studies of how bone marrow maintains hematopoietic stem cell function indicate that stromal cells were critically important for these stem cells, preventing apoptosis and providing signals for proliferation and differentiation, at times in coordination with the internal clock of the primitive cell. Stromal cells act through a number of mediators, cytokines, adhesion molecules, peptides, hormones, and other molecules. These cytokines and chemokines include the colony-stimulating factors; interleukins-1, -6, -7, and -8 (IL-1, IL-6, IL-7, IL-8); leukemia inhibitory factor; stem cell factor; flt3 ligand; hepatocyte growth factor; thrombopoietin; insulin-like growth factor-1; transforming growth factor  $\beta$  (TGF- $\beta$ ); tumor necrosis factor- $\alpha$  (TNF- $\alpha$ );  $\gamma$ -interferon-inducible protein-10 (IP-10); monocyte chemoattractant protein-1 (MCP-1); and stromal-derived factor-1. TGF- $\beta$  is the most potent inhibitor of hematopoiesis, which induces expression of inhibitory chemokines such as MCP-1 and IP-10 and decreases expression of stromal adhesion molecules. Together these signaling proteins make up the stem cell niche, a concept first expounded by Schofield in 1978 [37]. Schofield posited that when hematopoietic stem cells are fixed in a specific microenvironment they will maintain a stable potential for self-renewal, and that commitment to different hematopoietic lineages will be regulated by specific niches. The generation of continuous cloned murine marrow lines has confirmed the existence of niches [37]. Human stromal cells have been seen to home to and promote repair of pancreatic islets in NOD/scid mice, but no human cells have been detected in animal pancreases [38]. Therefore, improved pancreatic function in the mice suggests that stromal cells are able to establish a microenvironment conducive to the development of pancreatic islet  $\beta$  cells [38]. Friedenstein et al. provided the earliest evidence that adult bone marrow contains endothelial stem cells and primitive mesenchymal cells [39]. It is now well documented that bone marrow mesenchymal stem cells identified using positive markers for CD105 (SH2) and CD73 (SH3 and SH4) have the ability

to differentiate into multiple lineages, including osteogenic [40], adipogenic [41], and chondrogenic tissues [42]. Several mechanisms enable donor mesenchymal cells to evade host allogeneic responses [43,44]. Bone marrow mesenchymal cell-induced immunorejection tolerance of islet allograft has been observed *in vivo* through the induction of chimerism in the recipient [45]. Further research into these microenvironments will enable the development of interventions that reduce or prevent immunoreactions resulting in islet apoptosis or necrosis and the functional impairment of  $\beta$  cells [46].

### Bone Marrow and Islet Compatibility

Although it has been reported that bone marrow transplantation benefits diabetic animals *in vivo*, much debate surrounds the derivation of insulin-producing cells from bone marrow cells [47]. Bone marrow generated cells lack important characteristics of normal  $\beta$  cells, and much more information about the several possible mechanisms of regeneration which is needed. To name just one example, mice subjected to  $\beta$  cell damage were injected with labeled bone marrow cells. While no bone marrow cells were shown to develop into insulin-producing cells, many bone marrow-derived endothelial cells were present in areas of injury. The data therefore indicate that bone marrow-derived endothelial progenitor cells respond to  $\beta$  cell injury in the pancreas and that this mechanism might be beneficial in repairing islet damage or improving islet survival [48]. However, pure stem cell subpopulation from bone marrow cells pretreated under certainly condition can differentiate into positive insulin cells in pancreas *in vivo* [35]. The notion is further supported by bone marrow's role in pancreatic islet development during the neonatal period and after pancreatic injury [49].

### Human Islet is an Ideal Model in which to Study Fundamental Mechanisms of Islet Longevity

Recent evidence indicates that human islet differ significantly in morphology from islet in other species [50,51], which suggests that there is functional variation. If morphological variation between human islet and that of other species determines functional difference, therefore, human islets are probably the best model for determining how to ensure human islet survival *in vitro* and *in vivo*. In addition, we can examine mechanisms that regulate the islet survival process (or death process) relatively unencumbered by islet death-related pathologies, which are frequently confounding factors in diabetic studies. The knowledge generated from human islet model may also contribute to understanding the development of diabetes and possible strategies to prevent it.

### The Potential Mechanisms of Two Models of Bone Marrow Support of Islet Longevity

We have previously reported that allogeneic bone marrow supports human islet survival and function for more than six months [52]. Bone marrow reduces human islet release of IL-1 $\beta$ , thus abridging the apoptotic process in cultured islets (observed in our previous studies). Subsequent enlargement of cocultured islets suggests islet reconstitution and regeneration *in vitro* [53]. IL-1 $\beta$  expression and release in human islet  $\beta$  cells induced by islet injury can cause cell death by activating nuclear factor kappa B (NF- $\kappa$ B) and Fas apoptotic cascades to suppress islet function and to destroy  $\beta$  cells [54,55]. We propose two possible outcomes from reconstituting islets with allogeneic bone marrow in regard to islet longevity. In the template model, bone marrow cells transdifferentiate into islet cells after long-term culture, including bone

marrow progenitor cells, convert into epithelia and endothelia to form a biological islet capsule and/or  $\alpha$ ,  $\beta$ , or other endocrine cells [56]. Such cells would also have the bone marrow donor's HLA character, which will abrogate the induction of rejection if bone marrow-derived cells dominate the majority of reconstituted islets and the recipient is the bone marrow donor. In the nutrient model, bone marrow provides a supportive microenvironment by releasing/paracrine cytokines that stimulate islet cell regeneration and inhibition of the apoptotic process. In this model less change in the islets' immunological characteristics would be expected.

When human bone marrow is cocultured with islets, bone marrow-derived marrow stromal cells and/or lineage-positive cells release cytokines and other growth factors that stop the apoptotic process and stimulate islet cell self regeneration. Bone marrow-derived stem cells and/or mesenchymal cells, on the other hand, repair islet injury and aid islet reconstitution. By these two proposed models, bone marrow creates a microenvironment for islet regeneration that includes the formation of capsule-like tissue around islets and the potential for vascularization that will improve tolerance *in vitro* and implantation *in vivo* (See figure 1).

If bone marrow cells dominate the reconstituted islet population (template model), the islet tissue will have tolerance to bone marrow donor *in vivo*. If bone marrow cells only release factors to improve islet reconstitution (nutrient model), the reconstituted islets will have less tolerance to bone marrow donor cells *in vivo*. If the two models play an equal role, islet tissue implanted into bone marrow donor will improve tolerance (Figure 1).

### Cytokines TNF- $\alpha$ and IP-10 Play a Role in the Interaction of Bone Marrow and Islet Cells

We have proposed two mechanisms by which bone marrow culture may support repair and survival of human islet cells *in vitro*. We further propose that two cytokine/chemokines, tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) and chemokine IFN-gamma-inducible protein of 10 kDa (IP-10/CXCL10), may initiate the processes. TNF $\alpha$  plays an important known role in islet cell death by stimulating cellular apoptotic cascades. However, TNF $\alpha$ 's ability to generate an autocrine tumor-promoting network in epithelial ovarian cancer cells by stimulating the release of other cytokines and growth factors [57] from bone marrow suggests that TNF- $\alpha$  may also be the initiator of islet-supporting growth factor and cytokine release in bone marrow-derived lineage-positive and stromal cells, as outlined in our nutrient model. As the recruiter of

activated T lymphocytes to sites of inflammation by interaction with the G-protein-coupled receptor CXCR3, IP-10 has ability to stimulate cell migration by forming oligomers for presentation on endothelial cells and subsequent transendothelial migration, an essential step for lymphocyte recruitment *in vivo* [58]. However, high expression of CXCR3 in hematopoietic stem cells (HSCs) did not induce HSC migration [59], but IP-10 with overexpression of its receptor CXCR3 enhanced neural progenitor cell migration *in vitro* [60], suggesting that IP-10 may have other functions. We hypothesize that IP-10 may serve as an initiator for bone marrow mesenchymal cell differentiation into endothelia or epithelia, as outlined in our template model.

### Conclusion and Prospect for Future

We propose that bone marrow can be a solution for human islet  $\beta$ -cell longevity through cell-cell contact to participate in islet reconstitution and secretes or paracrine cytokines that appear to reduce production and release of inflammatory factors from islets, thus eliminating islet apoptosis. These events stimulate islet regeneration, recovery of insulin production, and eventually increase in islet mass. Bone marrow reconstituted human islet will have several important benefits: (a) more  $\beta$ -cells in islets will be generated from a limited resource; (b) islet proinflammatory factor production and release will be eliminated, resulting in decreased islet cell apoptosis and possible reduction of immunorejection *in vivo*; (c) islet remained survival will provide possibility for new approach to keeping islet longevity *in vitro* and *in vivo*.

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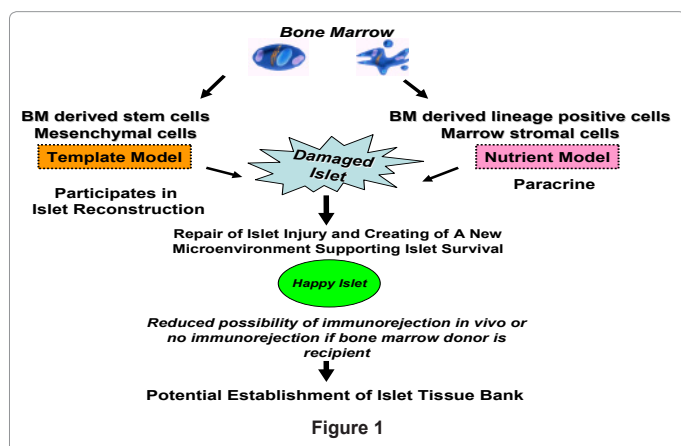


Figure 1

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