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Review

Islet Culture/Preservation Before Islet Transplantation

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Although islet culture prior to transplantation provides flexibility for the evaluation of isolated islets and the pretreatment of patients, it is well known that isolated islets deteriorate rapidly in culture. Human serum albumin (HSA) is used for medium supplementation instead of fetal bovine serum (FBS), which is typically used for islet culture research, to avoid the introduction of xenogeneic materials. However, FBS contains several factors that are beneficial to islet viability and which also neutralize the endogenous pancreatic enzymes or exogenous enzymes left over from the isolation process. Several groups have reported the comparison of cultures at 22°C and 37°C. Recent studies have demonstrated the superiority of 4°C preservation to 22°C and 37°C cultures. We herein review the current research on islet culture/preservation for clinical islet transplantation.

Key words: Islet transplantation; Culture condition; Preservation solution; University of Wisconsin (UW) solution; Low temperature

INTRODUCTION

After the introduction of the Edmonton protocol, pancreatic islet transplantation has emerged as one of the most promising therapeutic approaches for improving glycometabolic control in patients with type 1 diabetes (43,44). The Edmonton protocol originally required the infusion of islets into the recipient to occur within 4 h after isolation (43,44). Many centers have introduced the culturing of human islets prior to transplantation (12,14,22,42) because it provides many benefits to clinical islet transplantation, including additional quality control testing of the isolated islets, the ability to initiate time-dependent immunosuppressive protocols, and because it preserves the islets to allow recipients the time to travel to transplant centers, even if they live far away. However, it is well documented that isolated islets deteriorate rapidly in culture (15,21,22,35). This review describes the current research on islet culture/preservation for clinical islet transplantation.

SUPPLEMENTATION OF HUMAN SERUM ALBUMIN IN HUMAN ISLET CULTURE

A culture medium, which is a Connaught Medical Research Laboratories (CMRL)-based media containing 0.5–0.625% human serum albumin (HSA), has been used for clinical islet transplantation in many centers (15,34). Isolated islets from human pancreata are commonly cultured for 12–72 h at 22°C or at 37°C with 5% CO_2 in the culture medium before transplantation. The Edmonton group showed that, after culturing for 20 h (median), the islet equivalent (IEQ) yield significantly decreased from 363,309 ± 12,647 to 313,035 ± 10,862. Thirty-seven preparations suffered substantial islet loss (>20%), with three

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of the 104 preparations (3%) suffering an islet mass loss of >50%, necessitating the cancellation of the planned transplantations (22). Other centers have confirmed that major losses can occur in clinical-grade islet preparations (15,21). In our report on clinical islet transplantation from non-heart-beating donors, we found an approximately 30% decrease of IEQ after overnight culture (35). The supplementation of culture media with serum is generally considered to be better than supplementation with its albumin component alone because the serum contains many factors that are beneficial for islet viability (29) and because it neutralizes the endogenous pancreatic enzymes (4,13,40) or exogenous enzymes left over from the isolation process (4,13). Bucher et al. reported a lower level of apoptosis and a higher level of stimulated insulin secretion and insulin content when using 10% human AB serum instead of 0.625% HSA (6). Kerr-Conte et al. showed the higher viability, insulin content, and stimulation index of clinical-grade islets cultured for 5 days with 2.5% human AB serum in comparison to islets cultured in 0.625% HSA (20). Avgoustiniatos et al. showed that the average oxygen consumption rate per DNA content (OCR/DNA) was 27% higher with fetal bovine serum (FBS) supplementation than with HSA supplementation (3). However, FBS supplementation is undesirable because of the associated risk of the introduction of xenogeneic material into the clinical islet preparations, and it is difficult to obtain large amounts of human AB serum for clinical islet isolation and culture. Therefore, many centers continue to supplement clinical islet culture media with HSA.

ISLET CULTURE AT 22°C OR 37°C

Several reports have shown the comparison of 22–26°C (near room temperature) and 37°C cultures (5,8,24,37). Brandhorst et al. showed that 22°C cultures showed the increased survival of porcine islets and DNA recovery, but reduced 24-h insulin secretion in comparison to 37°C cultures (5). However, Ono et al. showed that increasing the temperature from 24°C to 37°C (24°C culture for 1–4 weeks followed by an increase of temperature to 37°C for 1 week) increased the rate of insulin release and that insulin secretion was comparable to that of islets that are maintained at 37°C (37). It has also been reported that central necrosis, which can be prevented at 22–26°C cultures, was observed in larger islets at 37°C cultures (5,24). Using clinical-grade pancreata, other studies have shown a significantly decreased preculture yield (15% loss) after culturing at 22°C for 20 h (median) (22). Similarly, 37°C culture for 32.5 h (median) was associated with a 20% loss in comparison to the preculture yield (15). Our group showed a 19% loss of islet mass in the 22°C culture and a 24% loss in the 37°C culture after 48 h (34). Itoh et al. showed that the rate of cell death in islets at 37°C was higher than that at 22°C under hypoxic conditions (1% O_2, 5% CO_2, and 94% N_2) (18). These reports suggest that islet culturing at 22–26°C may be superior to culturing at 37°C.

One of the mechanisms for the reduction in islet mass during culture is cell death by apoptosis and the prerecruitment of the intracellular death signaling pathways (1,2,7,19,31). Islets are susceptible to multiple insults during donor brain death (7), organ procurement, organ preservation, isolation (1), and in the culturing process itself. Studies have shown the absence of the peri-insular basement membrane immediately after isolation. This absence gives rise to an increase in pyknotic nuclei and apoptotic bodies, which is accompanied by the elevation of proapoptotic mitogen-activated protein kinase (MAPK) p38 and c-Jun NH2-terminal kinase (JNK) activity relative to prosurvival extracellular signal-regulated kinase (ERK1/2) activity (41). Some studies have confirmed the increased activity of JNK and p38 following isolation, which can be stimulated by cytokines such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) (2,19,31,38). Treatment with a JNK inhibitor during islet culture was shown, by our group and another group, to prevent the reduction in the number of islets and to enhance islet graft function in vivo (9,32,33). It has also been reported that the inhibition of p38 activation can reduce these proapoptotic activities (27,33,36,38). Antiapoptotic agents could prevent the reduction in islet mass during culture.

ISLET PRESERVATION AT 4°C

Only a few studies adequately evaluated lower temperature conditions in islet culture/preservation before our report. Frankel et al. reported the comparison of 8°C storage with 22°C or 37°C culture for 1 week using islets from obese (ob/ob) mice (10,11). They showed that the glucose-stimulated insulin release was better maintained by storage at 8°C in tissue culture medium with a high concentration (18 mM) of glucose and an additional preincubation period of 4 h at 37°C than by storage at 22°C or 37°C (10). In addition, 8°C storage in a high-potassium "intracellular medium" showed a better subsequent glucose-stimulated insulin release and islet morphology in comparison to a 37°C culture in traditional culture medium (11). Korbutt et al. reported the survival of rat pancreatic β-cells after 96 h of storage at 4°C (23). After 4°C storage in Collins solution with albumin and benzamidine, β-cells exhibited a higher insulin content than after culture in HAM's F10 at 20°C or 37°C, although their capacity for subsequent insulin synthesis and release was comparable (23). It was demonstrated that storage with University of Wisconsin (UW) solution plus pefabloc at 4°C was superior to culture at 20°C or 37°C; however, the experiments used unpurified islets (28).

Our report was the first to compare 22°C and 37°C cultures with 4°C preservation using purified human islets

(34). Our work clearly shows that 4°C storage in the UW solution was better than either the 22°C or 37°C culture (both in vitro and in vivo) (34). After our report, several groups showed the advantage of islet preservation at 4°C. Ikemoto et al. showed that the recovery rate of porcine islets was significantly higher at 4°C than at 37°C or 22°C (16). Ishii et al. reported that the islet yield in UW preservation at 4°C was maintained at a level that was comparable with that of fresh islets (but not in 37°C culture groups) (17). Itoh et al. showed that rate of cell death in islets at 4°C was lower than that at 37°C under hypoxic conditions (1% O_2, 5% CO_2, and 94% N_2) and that streptozotocin (STZ)-induced diabetic mice were ameliorated after receiving hypoxia-4°C islets but not after receiving hypoxia-37°C and hypoxia-22°C islets (18). Moreover, they showed that the levels of released high mobility group box 1 (HMGB1), granulocyte-colony-stimulating factor (G-CSF), keratinocyte chemoattractant (KC), regulated upon activation, normal T cell expressed, and secreted (RANTES), monocyte chemotactic protein-1 (MCP-1), and macrophage inflammatory protein-1α (MIP-1α) were significantly reduced in the hypoxia-4°C islets in comparison to the levels in hypoxia-37°C islets. Liu et al. reported that a 4°C group showed a higher recovery rate of islet quantity, a lower percentage of propidium iodide (PI)-positive area, better insulin release ability, and lower expression levels of hypoxia inducible factor-1α (HIF-1α) and B cell CLL/lymphoma 2-associated X protein (Bax) in comparison to a 37°C group (26).

The islet diameter after 22°C and 37°C cultures was shown to become smaller than that in fresh islets by Kin et al. and our group (22,34), suggesting that the main reason for the reduction in islet yield during culture is the reduction in islet diameter. However, after 4°C preservation in UW solution, the islet diameter and morphology were similar to those of fresh islets (34). Moreover, the morphology of acinar cells after 4°C preservation was also similar to that of fresh tissue (34). Harmful enzymes that are released from dying acinar cells during culture may be deleterious to islet cell survival, especially when using culture media with HSA supplementation rather than serum. It has been reported that acinar tissue does not survive well in culture (25), while the purity after culture is higher than that of fresh islets. In addition, a lower islet purity may result from greater islet loss during culture (22). One of the advantages of 4°C preservation may be the prevention of acinar cell deterioration and/or inactivation of harmful enzymes (due to the low temperature), even if they are released by the dying acinar cells.

CONCLUSION

Current isolation techniques usually recover fewer than half of the islets from a given pancreas, necessitating islet transplantation from two or more donors to achieve euglycemia (30,43). Moreover, barely half of the processed pancreata meet the criteria for clinical transplantation in most centers. Thus, islet losses during culture result in an even lower transplant rate. Islet cells that are cultured at 37°C have a higher oxygen requirement than islets preserved at 4°C. In the current clinical culture conditions, it seems that islets cultured at 37°C cannot receive enough oxygen because we frequently observed central necrosis of islets during culture. In addition, non-endocrine cells produce a higher amount of cytokines/chemokines (such as trypsin), which induce the deterioration of islet cells. The low-temperature inhibition of cytokine/chemokine activity may be another advantage of 4°C preservation. However, one of the advantages for 22°C and 37°C culture is the reduction of transplanted tissue volume due to the elimination of acinar cells and/or dead cells. One of the ideas behind islet culture is to select healthy islets from predamaged ones in order to minimize proinflammatory and proapoptotic effects in the graft (39). Moreover, culture at room temperature was initially introduced as a means of reducing islet antigenicity (24,37). A future study should carefully evaluate the effects of islet equivalent and tissue volume in relation to the antigenicity of 4°C-preserved islets.

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REFERENCES

1. Abdelli, S.; Ansite, J.; Roduit, R.; Borsello, T.; Matsumoto, I.; Sawada, T.; Allaman-Pillet, N.; Henry, H.; Beckmann, J. S.; Hering, B. J.; Bonny, C. Intracellular stress signaling pathways activated during human islet preparation and following acute cytokine exposure. Diabetes 53:2815–2823; 2004.
2. Ammendrup, A.; Maillard, A.; Nielsen, K.; Aabenhus Andersen, N.; Serup, P.; Dragsbaek Madsen, O.; Mandrup-Poulsen, T.; Bonny, C. The c-Jun amino-terminal kinase pathway is preferentially activated by interleukin-1 and controls apoptosis in differentiating pancreatic beta-cells. Diabetes 49:1468–1476; 2000.
3. Avgoustiniatos, E. S.; Scott, 3rd., W. E.; Suszynski, T. M.; Schuurman, H. J.; Nelson, R. A.; Rozak, P. R.; Mueller, K. R.; Balamurugan, A. N.; Ansite, J. D.; Fraga, D. W.; Friberg, A. S.; Wildey, G. M.; Tanaka, T.; Lyons, C. A.; Sutherland, D. E.; Hering, B. J.; Papas, K. K. Supplements in human islet culture: Human serum albumin is inferior to fetal bovine serum. Cell Transplant. 21:2805–2814; 2012.
4. Balamurugan, A. N.; He, J.; Guo, F.; Stolz, D. B.; Bertera, S.; Geng, X.; Ge, X.; Trucco, M.; Bottino, R. Harmful delayed effects of exogenous isolation enzymes on isolated human islets: Relevance to clinical transplantation. Am. J. Transplant. 5:2671–2681; 2005.
5. Brandhorst, D.; Brandhorst, H.; Hering, B. J.; Bretzel, R. G. Long-term survival, morphology and in vitro function of isolated pig islets under different culture conditions. Transplantation 67:1533–1541; 1999.
6. Bucher, P.; Bosco, D.; Mathe, Z.; Matthey-Doret, D.; Buhler, A. L.; Morel, P.; Berney, T. Human islet culture

before transplantation: Influence of medium on islet apoptosis and function. Transplantation 76:S65–S66; 2003.
7. Contreras, J. L.; Eckstein, C.; Smyth, C. A.; Sellers, M. T.; Vilatoba, M.; Bilbao, G.; Rahemtulla, F. G.; Young, C. J.; Thompson, J. A.; Chaudry, I. H.; Eckhoff, D. E. Brain death significantly reduces isolated pancreatic islet yields and functionality in vitro and in vivo after transplantation in rats. Diabetes 52:2935–2942; 2003.
8. Cui, Y. F.; Ma, M.; Wang, G. Y.; Han, D. E.; Vollmar, B.; Menger, M. D. Prevention of core cell damage in isolated islets of Langerhans by low temperature preconditioning. World J. Gastroenterol. 11:545–550; 2005.
9. Fornoni, A.; Pileggi, A.; Molano, R. D.; Sanabria, N. Y.; Tejada, T.; Gonzalez-Quintana, J.; Ichii, H.; Inverardi, L.; Ricordi, C.; Pastori, R. L. Inhibition of c-jun N terminal kinase (JNK) improves functional beta cell mass in human islets and leads to AKT and glycogen synthase kinase-3 (GSK-3) phosphorylation. Diabetologia 51:298–308; 2008.
10. Frankel, B. J.; Gylfe, E.; Hellman, B.; Idahl, L. A. Maintenance of insulin release from pancreatic islets stored in the cold for up to 5 weeks. J. Clin. Invest. 57:47–52; 1976.
11. Frankel, B. J.; Norlund, N. R. Cold storage (8 C) of islets of Langerhans in a high-potassium "intracellular medium": Near-normal insulin release and morphology after one week. J. Endocrinol. Invest. 8:59–62; 1985.
12. Froud, T.; Ricordi, C.; Baidal, D. A.; Hafiz, M. M.; Ponte, G.; Cure, P.; Pileggi, A.; Poggioli, R.; Ichii, H.; Khan, A.; Ferreira, J. V.; Pugliese, A.; Esquenazi, V. V.; Kenyon, N. S.; Alejandro, R. Islet transplantation in type 1 diabetes mellitus using cultured islets and steroid-free immunosuppression: Miami experience. Am. J. Transplant. 5:2037–2046; 2005.
13. Goto, M.; Eich, T. M.; Felldin, M.; Foss, A.; Källen, R.; Salmela, K.; Tibell, A.; Tufveson, G.; Fujimori, K.; Engkvist, M.; Korsgren, O. Refinement of the automated method for human islet isolation and presentation of a closed system for in vitro islet culture. Transplantation 78:1367–1375; 2004.
14. Hering, B. J.; Kandaswamy, R.; Harmon, J. V.; Ansite, J. D.; Clemmings, S. M.; Sakai, T.; Paraskevas, S.; Eckman, P. M.; Sageshima, J.; Nakano, M.; Sawada, T.; Matsumoto, I.; Zhang, H. J.; Sutherland, D. E.; Bluestone, J. A. Transplantation of cultured islets from two-layer preserved pancreases in type 1 diabetes with anti-CD3 antibody. Am. J. Transplant. 4:390–401; 2004.
15. Ichii, H.; Sakuma, Y.; Pileggi, A.; Fraker, C.; Alvarez, A.; Montelongo, J.; Szust, J.; Khan, A.; Inverardi, L.; Naziruddin, B.; Levy, M. F.; Klintmalm, G. B.; Goss, J. A.; Alejandro, R.; Ricordi, C. Shipment of human islets for transplantation. Am. J. Transplant. 7:1010–1020; 2007.
16. Ikemoto, T.; Noguchi, H.; Fujita, Y.; Takita, M.; Shimoda, M.; Sugimoto, K.; Jackson, A.; Naziruddin, B.; Shimada, M.; Levy, M. F.; Matsumoto, S. New stepwise cooling system for short-term porcine islet preservation. Pancreas 39:960–963; 2010.
17. Ishii, S.; Saito, T.; Ise, K.; Yamashita, M.; Sato, Y.; Saito, T.; Tsukada, M.; Oshibe, I.; Kenjo, A.; Kimura, T.; Anazawa, T.; Suzuki, S.; Gotoh, M. Preservation of pancreatic islets in cold UW solution before transplantation. Islets 4:32–39; 2012.
18. Itoh, T.; Sugimoto, K.; Takita, M.; Shimoda, M.; Chujo, D.; SoRelle, J. A.; Naziruddin, B.; Levy, M. F.; Matsumoto, S. Low temperature condition prevents hypoxia-induced islet cell damage and HMGB1 release in a mouse model. Cell Transplant. 21:1361–1370; 2012.
19. Kaneto, H.; Xu, G.; Fujii, N.; Kim, S.; Bonner-Weir, S.; Weir, G. C. Involvement of c-Jun N-terminal kinase in oxidative stress-mediated suppression of insulin gene expression. J. Biol. Chem. 277:30010–30018; 2002.
20. Kerr-Conte, J.; Vandewalle, B.; Moerman, E.; Lukowiak, B.; Gmyr, V.; Arnalsteen, L.; Caiazzo, R.; Sterkers, A.; Hubert, T.; Vantyghem, M. C.; Pattou, F. Upgrading pretransplant human islet culture technology requires human serum combined with media renewal. Transplantation 89:1154–1160; 2010.
21. Keymeulen, B.; Gillard, P.; Mathieu, C.; Movahedi, B.; Maleux, G.; Delvaux, G.; Ysebaert, D.; Roep, B.; Vandemeulebroucke, E.; Marichal, M.; In 't Veld, P.; Bogdani, M.; Hendrieckx, C.; Gorus, F.; Ling, Z.; van Rood, J.; Pipeleers, D. Correlation between beta cell mass and glycemic control in type 1 diabetic recipients of islet cell graft. Proc. Natl. Acad. Sci. USA 103:17444–17449; 2006.
22. Kin, T.; Senior, P.; O'Gorman, D.; Richer, B.; Salam, A.; Shapiro, A. M. Risk factors for islet loss during culture prior to transplantation. Transpl. Int. 21:1029–1035; 2008
23. Korbutt, G. S.; Pipeleers, D. G. Cold-preservation of pancreatic beta cells. Cell Transplant. 3:291–297; 1994.
24. Lacy, P. E.; Davie, J. M.; Finke, E. H. Prolongation of islet xenograft survival without continuous immunosuppression. Science 209:283–285; 1980.
25. Lardon, J.; De Breuck, S.; Rooman, I.; Van Lommel, L.; Kruhøffer, M.; Orntoft, T.; Schuit, F.; Bouwens, L. Plasticity in the adult rat pancreas: Transdifferentiation of exocrine to hepatocyte-like cells in primary culture. Hepatology 39:1499–1507; 2004.
26. Liu, F.; Tian, W.; Yang, Y.; Zhang, Q.; Zhu, M.; Yang, L.; Yang, L.; Li, J.; Liu, J.; Wu, P.; Yang, K.; Wang, X.; Shen, Y.; Qi, Z. Optimal method for short-term or long-term islet preservation: Comparison of islet culture, cold preservation and cryopreservation. J. Artif. Organs 17:337–343; 2014.
27. Matsuda, T.; Omori, K.; Vuong, T.; Pascual, M.; Valiente, L.; Ferreri, K.; Todorov, I.; Kuroda, Y.; Smith, C. V.; Kandeel, F.; Mullen, Y. Inhibition of p38 pathway suppresses human islet production of pro-inflammatory cytokines and improves islet graft function. Am. J. Transplant. 5:484–493; 2005.
28. Matsumoto, S.; Lawrence, O.; Rigley, T. H.; Lakey, J. R.; Stevens, R. B.; Strong, D. M. University of Wisconsin solution with trypsin inhibitor pefabloc improves survival of viable human and primate impure islets during storage. Cell Tissue Bank. 2:15–21; 2001.
29. Murdoch, T. B.; McGhee-Wilson, D.; Shapiro, A. M.; Lakey, J. R. Methods of human islet culture for transplantation. Cell Transplant. 13:605–617; 2004.
30. Nano, R.; Clissi, B.; Melzi, R.; Calori, G.; Maffi, P.; Antonioli, B.; Marzorati, S.; Aldrighetti, L.; Freschi, M.; Grochowiecki, T.; Socci, C.; Secchi, A.; Di Carlo, V.; Bonifacio, E.; Bertuzzi, F. Islet isolation for allotransplantation: Variables associated with successful islet yield and graft function. Diabetologia 48:906–912; 2005.
31. Noguchi, H.; Matsumoto, S.; Onaca, N.; Naziruddin, B.; Jackson, A.; Ikemoto, T.; Shimoda, M.; Fujita, Y.; Chujo, D.; Iwanaga, Y.; Nagata, H.; Okitsu, T.; Kobayashi, N.; Ueno, H.; Chaussabel, D.; Grayburn, P.; Banchereau, J.; Levy, M. F. Ductal injection of JNK inhibitors before pancreas preservation prevents islet apoptosis and improves islet graft function. Hum. Gene Ther. 20:73–85; 2009.

32. Noguchi, H.; Nakai, Y.; Matsumoto, S.; Kawaguchi, M.; Ueda, M.; Okitsu, T.; Iwanaga, Y.; Yonekawa, Y.; Nagata, H.; Minami, K.; Masui, Y.; Futaki, S.; Tanaka, K. Cell permeable peptide of JNK inhibitor prevents islet apoptosis immediately after isolation and improves islet graft function. Am. J. Transplant. 5:1848–1855; 2005.
33. Noguchi, H.; Nakai, Y.; Ueda, M.; Masui, Y.; Futaki, S.; Kobayashi, N.; Hayashi, S.; Matsumoto S. Activation of c-Jun NH2-terminal kinase (JNK) pathway during islet transplantation and prevention of islet graft loss by intraportal injection of JNK inhibitor. Diabetologia 50:612–619; 2007.
34. Noguchi, H.; Naziruddin, B.; Jackson, A.; Shimoda, M.; Ikemoto, T.; Fujita, Y.; Chujo, D.; Takita, M.; Kobayashi, N.; Onaca, N.; Levy, M. F.; Matsumoto, S. Low-temperature preservation of isolated islets is superior to conventional islet culture before islet transplantation. Transplantation 89:47–54; 2010.
35. Noguchi, H.; Yamada, Y.; Okitsu, T.; Iwanaga, Y.; Nagata, H.; Kobayashi, N.; Hayashi, S.; Matsumoto, S. Secretory Unit of Islet in Transplantation (SUIT) and Engrafted Islet Rate (EIR) indexes are useful for evaluating single islet transplantation. Cell Transplant. 17:121–128; 2008.
36. Omori, K.; Todorov, I.; Shintaku, J.; Rawson, J.; Al-Abdullah, I. H.; Higgins, L. S.; Medicherla, S.; Kandeel, F.; Mullen, Y. P38alpha-selective mitogen-activated protein kinase inhibitor for improvement of cultured human islet recovery. Pancreas 39:436–443; 2010.
37. Ono, J.; Lacy, P. E.; Michael, H. E.; Greider, M. H. Studies of the functional and morphologic status of islets maintained at 24 C for four weeks in vitro. Am. J. Pathol. 97:489–503; 1979.
38. Paraskevas, S.; Aikin, R.; Maysinger, D.; Lakey, J. R.; Cavanagh, T. J.; Agapitos, D.; Wang, R.; Rosenberg, L. Modulation of JNK and p38 stress activated protein kinases in isolated islets of Langerhans: Insulin as an autocrine survival signal. Ann. Surg. 233:124–133; 2001.
39. Rijkelijkhuizen, J. K.; van der Burg, M. P.; Töns, A.; Terpstra, O. T.; Bouwman, E. Pretransplant culture selects for high-quality porcine islets. Pancreas 32:403–407; 2006.
40. Rose, N. L.; Palcic, M. M.; Lakey, J. R. An evaluation of endogenous pancreatic enzyme levels after human islet isolation. Pancreas 27:167–173; 2003.
41. Rosenberg, L.; Wang, R.; Paraskevas, S.; Maysinger, D. Structural and functional changes resulting from islet isolation lead to islet cell death. Surgery 126:393–398; 1999.
42. Ryan, E. A.; Paty, B. W.; Senior, P. A.; Bigam, D.; Alfadhli, E.; Kneteman, N. M.; Lakey, J. R.; Shapiro, A. M. Five-year follow-up after clinical islet transplantation. Diabetes 54:2060–2069; 2005.
43. Shapiro, A. M.; Lakey, J. R.; Ryan, E. A.; Korbutt, G. S.; Toth, E.; Warnock, G. L.; Kneteman, N. M.; Rajotte, R. V. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N. Engl. J. Med. 343:230–238; 2000.
44. Shapiro, A. M.; Ricordi, C.; Hering, B. J.; Auchincloss, H.; Lindblad, R.; Robertson, R. P.; Secchi, A.; Brendel, M. D.; Berney, T.; Brennan, D. C.; Cagliero, E.; Alejandro, R.; Ryan, E. A.; DiMercurio, B.; Morel, P.; Polonsky, K. S.; Reems, J. A.; Bretzel, R. G.; Bertuzzi, F.; Froud, T.; Kandaswamy, R.; Sutherland, D. E.; Eisenbarth, G.; Segal, M.; Preiksaitis, J.; Korbutt, G. S.; Barton, F. B.; Viviano, L.; Seyfert-Margolis, V.; Bluestone, J.; Lakey, J. R. International trial of the Edmonton protocol for islet transplantation. N. Engl. J. Med. 355:1318–1330; 2006.