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Bibliometric analysis of the top-cited articles on islet transplantation

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Abstract

Aims: To identify and characterize the top-cited articles in the field of islet transplantation.

Methods: We used the Science Citation Index Expanded database to identify the most frequently cited articles published after 1900. Articles were evaluated using the following characteristics: citation number, publication year, study design, references, country and institution of origin, authorship, and journal. Keyword analysis and citation networks were used to analyze research trends.

Results: The most frequently cited articles received between 146 and 2988 citations; the median was 291. All of the most frequently cited articles were published between 1972 and 2012, and 85 articles were published after 1990. The most popular study design involved basic science (75 articles). The leading countries were the United States (US) and Canada, and the leading institutions were the University of Alberta, Canada, and the University of Minnesota, in the US. Journals specializing in diabetes or transplantation published more than half of the articles (n = 53, 52%), with the journal *Diabetes* publishing the largest number (n = 30). No association was found between a journal's impact factor and the number of top-cited articles it published. There was no correlation between the number of citations and the number of years since publication, authors, participating institutions, or countries involved. Top-cited articles focused on 2 themes: the use of antirejection immunotherapy or biocompatible encapsulations to prolong graft survival, and assessments of the efficacy of islet transplants, in particular, islet allografts.

Conclusions: Our study can help researchers to identify and decipher the characteristics of top-cited articles in the field of islet transplantation. Just as clinically successful allografts are carried out using the Edmonton protocol, autografts and xenografts should be similarly strengthened to solve problems relating to immune rejection and islet sources, respectively.

Abbreviations: PNAS = Proceedings of the National Academy of Sciences, RCT = randomized controlled trial, US = United States.

Keywords: bibliometrics, citation analysis, citation classics, islet transplantation

1. Introduction

Diabetes now affects 382 million people and causes approximately 4.6 million deaths every year globally.[1,2] It is also a major risk factor for cardiovascular disease, stroke, renal failure, blindness, and lower limb amputation. In various treatments for diabetes, islet transplantation may be the most promising strategy for clinically curing this condition, particularly in the case of type 1 diabetes mellitus.[3,4] Many articles on islet transplantation have been published during the past decades, and the number continues to increase. Top-cited articles (also called classic articles or citation classics) in the field of islet transplantation have not been identified or characterized, despite their importance in promoting the development of islet transplantation.

The number of citations an article receives after publication is an important measure of its significance within the scientific community, because the influence of a paper in a particular discipline is usually proportional to the number of citations it receives.[5] Citation analysis is therefore one method of bibliometric analysis that has been used to quantify the relative importance of a scientific paper by examining the citations attributed to that paper.[6,7] Recently, top-cited articles have been identified using citation analysis in many medical fields, including head and neck surgery, lumbar spine surgery, plastic surgery, orthopedic elbow surgery, neurosurgery, hand surgery, diabetes, and hypertension.[8–17] As far as we know, this type of identification has not been used in the field of islet transplantation. In this bibliometric study, we have carried out a citation analysis to identify and characterize the 100 most frequently cited articles on islet transplantation.

2. Methods

2.1. Study design and data search

We used the Science Citation Index Expanded (SCIE, 1900–2017) database to identify the 100 most frequently cited articles in islet transplantation research because this platform has been

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Q-HP and Q-JL contributed equally to this work.

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The authors have declared no conflicts of interest.

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used to identify top-cited articles in many other medical specialties.[10,14,15,18] Search expressions included the following terms and Boolean operators: "transplant*" OR "graft*" OR "autotransplant*" OR "autograft*" OR "isotransplant*" OR "isograft*" OR "allotransplant*" OR "allograft*" OR "homotransplant*" OR "homograft*" OR "heterotransplant*" OR "heterograft*" OR "xenotransplant*" OR "xenograft*". These were used to retrieve the transplantation research. To identify studies about islets, the Boolean operator "AND" was added to the transplantation-specific terms, followed by the search terms ("islet*"OR ("island*" and "pancrea*") OR ("island*" and "Langerhans")). The search, performed on May 7, 2017, yielded a complete list of articles on islet transplantation. No language was restricted in this search. Ethical approval was not required in this study, because no patients were enrolled.

2.2. Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) papers focusing on islet transplantation as the main topic; (2) original articles and reviews. The exclusion criteria were as follows: (1) articles focused on broad areas, with no emphasis on islet transplantation; (2) articles focused on transplantations of other organs or cells, such as heart, liver, kidney, lung, or stem cell transplants; (3) meeting abstracts, letters, editorial materials, corrections, book chapters, errata, discussions, and book reviews.

2.3. Identification and assessment of the top 100 articles

To ensure a consistency of data abstraction, we used the method developed by Lim et al.[19] Three investigators (QHP, QJL, and HL), including 1 clinical pharmacist and 2 physicians in the field of endocrinology (with 10, 11, and 3 years of experience, respectively), initially reviewed the same 150 articles on islet transplantation which were randomly chosen. Any disagreements were resolved in a consensus meeting consisting of 4 authors (QHP, QJL, HL, and KHF). Although no formal interobserver reliability testing was conducted between the investigators, the disagreements were even rare. After initial pilot training, the searched results were manually assessed by 3 independent authors (QHP, QJL, and HL).

The search results were arranged from most to least citations using the "times cited" option. Later, the results were assessed by 3 independent authors (QHP, QJL, and HL) to compile 1 comprehensive list of the 100 most frequently cited articles. Finally, the top 100 articles were reviewed and data were extracted, in accordance with the method developed by Azer and Azer.[20]

The 100 selected articles were analyzed using the following parameters: citation number, publication year, study design, references, country and institution of origin, authorship, and journal. Citation numbers for the top 100 articles were obtained by searching the SCOPUS database. Numbers listed only in the SCIE database were not included. In addition to a randomized controlled trial (RCT), this study incorporated other study designs, such as nonrandomized controlled and uncontrolled trials, including cohort, case-control, and cross-sectional studies, and a case series. Articles were grouped into the following six6 categories by study design and goal: (1) a RCT; (2) an observational study including cohort, case-control, and cross-sectional studies, and a case series; (3) basic science, including bench-top laboratory research and research involving animal or cell models; (4) a review; (5) a meta-analysis; and (6) clinical guidelines. Once a list of journal impact factors had been obtained from the Journal Citation Report 2016, we studied the correlation between each journal's impact factor and the number of top 100 articles it published. We also investigated the correlation between the number of citations and other characteristics, namely, the number of years since publication, and the number of authors, participating countries, and institutions involved. SCIE reference data were used to complete the reference analysis. Because keywords were separated into different time periods to demonstrate trend variations on research topics in the fields of lung cancer and obstructive sleep apnea, the combined analysis of author keywords and keywords plus in SCIE database demonstrated research trends in islet transplantation. [21,22] To visualize the citation links and research topics of the 100 most frequently cited articles, we used CitNetExplorer Software version 1.0 to carry out a citation network analysis, using Kusumastuti et al's[23] method. Lastly, we chose Oxford Centre for Evidence-based Medicine—Levels of Evidence (2009 edition) to assess the top-cited articles.

2.4. Statistical analyses

All data were analyzed using GraphPad Prism software (version 6, GraphPad Software Inc. CA). Nonparametric Spearman rank correlations were used to determine the correlations among variables. All statistical tests were 2-tailed; a P value of $<.05$ was considered statistically significant.

3. Results

3.1. Citations

Table 1 shows the top-cited articles in islet transplantation research in descending order, according to total citations. Two other articles had the same number of citations as the paper ranked 100, bringing the total number of articles to 102. The median number of citations for the top 100 articles was 291 (range 146–2988). We found a generally positive correlation between the total number of citations in SCIE, citation density (citations per year), and citations in SCOPUS ($r=0.63$, $P<.05$; $r=0.82$, $P<.05$).The same article had the highest number of citations in SCIE and SCOPUS, and the highest citation density: a clinical trial about islet transplantation in seven patients with type 1 diabetes mellitus using glucocorticoid-free immunosuppressive regimen, published in the *New England Journal of Medicine* in 2000 by Shapiro et al.[24] All articles were published in the English language. We also analyzed references in the top 100 articles using SCIE data. The reference numbers for these studies ranged from 4 to 180, with an average of 39 references. Further analysis demonstrated that 9 references were high-frequency (≥10 times) (Table 2); 5 of these were included in the top 100 articles. Interestingly, the article published in the *New England Journal of Medicine* in 2000 by Shapiro et al[24] was still ranked number 1 (having been cited 23 times). In addition, 4 high-frequency references were related to the method of islet isolation.

3.2. Publication year, study design, and levels of evidence of the top-cited articles

These articles were published over a 40-year period (from 1972 to 2012). Figure 1A shows the distribution of top-cited articles by decade of publication. The largest group of articles (47) was published in the 1990s; overall, 85 articles were published after

Table 1

The top-cited articles in islet transplantation research.

Rank	Article	Study design	Citations in SCIE	Citations per year	Citations in SCOPUS
1	Shapiro AMJ, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *New England Journal of Medicine* 2000; 343(4):230-238	Observational study	2988	176	3498
2	Lenschow DJ, et al. Long-term survival of xenogeneic pancreatic-islet grafts induced by CTLA4IG. *Science* 1992; 257(5071):789-792	Basic science	1100	44	957
3	Shapiro AMJ, et al. International trial of the Edmonton protocol for islet Transplantation. *New England Journal of Medicine* 2006; 355(13):1318-1330	Observational study	1002	91	1071
4	Ryan EA, et al. Five-year follow-up after clinical islet Transplantation. *Diabetes* 2005; 54(7):2060-2069	Observational study	945	79	1068
5	Bonner-Weir S, et al. In vitro cultivation of human islets from expanded ductal tissue. *Proceedings of The National Academy of Sciences (PNAS)* 2000; 97(14):7999-8004.	Basic science	694	41	816
6	Inoguchi T, et al. Preferential elevation of protein-kinase-C isoform-beta-II and diacylglycerol levels in the aorta and heart of diabetic rats: differential reversibility to glycemic control by islet cell Transplantation. *Proceedings of The National Academy of Sciences (PNAS)* 1992; 89(22):11059-11063	Basic science	605	24	614
7	Ryan EA, et al. Clinical outcomes and insulin secretion after islet transplantation with the Edmonton protocol. *Diabetes* 2001; 50(4):710-719	Observational study	574	36	660
8	Ballinger WF, et al. Transplantation of intact pancreatic-islets in rats. *Surgery* 1972; 72 (2):175-186	Basic science	518	12	395
9	Ryan EA, et al. Successful islet transplantation - continued insulin reserve provides long-term glycemic control. *Diabetes* 2002; 51(7):2148-2157	Observational study	465	31	565
10	Gregori S, et al. Regulatory T cells induced by 1 alpha,25-dihydroxyvitamin D-3 and mycophenolate mofetil treatment mediate transplantation tolerance. *Journal of Immunology* 2001; 167(4):1945-1953	Basic science	427	27	465
11	Posselt AM, et al. Induction of donor-specific unresponsiveness by intrathymic islet transplantation. *Science* 1990; 249(4974):1293-1295	Basic science	413	15	319
12	Soonshiong P, et al. Insulin independence in a type-1 diabetic patient after encapsulated islet Transplantation. *Lancet* 1994; 343(8903):950-951	Observational study	403	18	448
13	Lau HT, et al. Prevention of islet allograft rejection with engineered myoblasts expressing FasL in mice. *Science* 1996; 273(5271):109-112	Basic science	391	19	394
14	Kang SM, et al. Fas ligand expression in islets of Langerhans does not confer immune privilege and instead targets them for rapid destruction. *Nature Medicine* 1997; 3 (7):738-743	Basic science	388	19	400
15	Farilla L, et al. Glucagon-like peptide 1 inhibits cell apoptosis and improves glucose responsiveness of freshly isolated human islets. *Endocrinology* 2003; 144(12):5149-5158	Basic science	375	27	448
16	Faustman D, et al. Prolongation of murine islet allograft survival by pretreatment of islets with antibody directed to ia determinants. *Proceedings of The National Academy of Sciences (PNAS)* 1981; 78(8):5156-5159	Basic science	356	10	185
17	Lacy PE, et al. Prolongation of islet allograft survival following invitro culture (24-degrees-c) and a single injection of ALS. *Science* 1979; 204(4390): 312-313	Basic science	345	9	191
18	Parker DC, et al. Survival of mouse pancreatic-islet allografts in recipients treated with allogeneic small lymphocytes and antibody to CD40 ligand. *Proceedings of The National Academy of Sciences (PNAS)* 1995; 92(21):9560-9564	Basic science	344	16	346
19	Hering BJ, et al. Single-donor, marginal-dose islet transplantation in patients with type 1 Diabetes. *JAMA* 2005; 293(7):830-835	Observational study	330	28	371
20	Kemp CB, et al. Effect of transplantation site on results of pancreatic-islet isografts in diabetic rats. *Diabetologia* 1973; 9(6):486-491	Basic science	324	7	207
21	Davalli AM, et al. Vulnerability of islets in the immediate posttransplantation period - dynamic changes in structure and function. *Diabetes* 1996; 45(9):1161-1167	Basic science	322	15	332
22	Moberg L, et al. Production of tissue factor by pancreatic islet cells as a trigger of detrimental thrombotic reactions in clinical islet Transplantation. *Lancet* 2002; 360 (9350):2039-2045	Basic science	321	21	337
23	Kenyon NS, et al. Long-term survival and function of intrahepatic islet allografts in rhesus monkeys treated with humanized anti-CD154. *Proceedings of The National Academy of Sciences (PNAS)* 1999; 96(14):8132-8137	Basic science	319	18	334
24	Hering BJ, et al. Prolonged diabetes reversal after intraportal xenotransplantation of wild-type porcine islets in immunosuppressed nonhuman primates. *Nature Medicine* 2006; 12(3):301-303	Basic science	317	29	336

(*continued*)

Table 1
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Rank	Article	Study design	Citations in SCIE	Citations per year	Citations in SCOPUS
25	Allison J, et al. Transgenic expression of CD95 ligand on islet beta cells induces a granulocytic infiltration but does not confer immune privilege upon islet allografts. *Proceedings of The National Academy of Sciences (PNAS)* 1997; 94(8):3943-3947	Basic science	315	16	316
26	Sun YL, et al. Normalization of diabetes in spontaneously diabetic cynomologus monkeys by xenografts of microencapsulated porcine islets without immunosuppression. *Journal of Clinical Investigation* 1996; 98(6):1417-1422	Basic science	300	14	335
27	Faustman DL, et al. Prevention of rejection of murine islet allografts by pretreatment with anti-dendritic cell antibody. *Proceedings of The National Academy of Sciences (PNAS)* 1984; 81(12):3864-3868	Basic science	293	9	185
28	Scharp DW, et al. Insulin independence after islet transplantation into type-I diabetic patient. *Diabetes* 1990; 39(4):515-518	Observational study	287	11	262
29	Cardona K, et al. Long-term survival of neonatal porcine islets in nonhuman primates by targeting costimulation pathways. *Nature Medicine* 2006; 12(3):304-306	Basic science	281	26	290
30	Heneine W, et al. No evidence of infection with porcine endogenous retrovirus in recipients of porcine islet-cell xenografts. *Lancet* 1998; 352(9129):695-699	Basic science	271	14	294
31	Lacy PE, et al. Maintenance of normoglycemia in diabetic mice by subcutaneous xenografts of encapsulated islets. *Science* 1991; 254(5039):1782-1784	Basic science	263	10	251
32	Robertson RP, et al. Medical progress: islet transplantation as a treatment for diabetes - a work in progress. *New England Journal of Medicine* 2004; 350(7):694-705	Review	262	20	298
33	Dionne KE. Effect of hypoxia on insulin-secretion by isolated rat and canine islets of Langerhans. *Diabetes* 1993; 42(1):12-21	Basic science	262	11	278
34	Bennet W, et al. Incompatibility between human blood and isolated islets of Langerhans - a finding with implications for clinical intraportal islet transplantation? *Diabetes* 1999; 48(10):1907-1914	Basic science	255	14	274
35	Barton FB, et al. Improvement in outcomes of clinical islet transplantation: 1999–2010. *Diabetes Care* 2012; 35(7):1436-1445	Observational study	254	51	287
36	Mauer SM, et al. Studies of rate of regression of glomerular lesions in diabetic rats treated with pancreatic-islet Transplantation. *Diabetes* 1975; 24(3):280-285	Basic science	249	6	138
37	Eizirik DL, et al. Prolonged exposure of human pancreatic-islets to high glucose-concentrations invitro impairs the beta-cell function. *Journal of Clinical Investigation* 1992; 90(4):1263-1268	Basic science	241	10	229
38	Tzakis AG, et al. Pancreatic-islet transplantation after upper abdominal exenteration and liver replacement. *Lancet* 1990; 336(8712):402-405	Observational study	241	9	183
39	Scharp DW, et al. Results of our 1st 9 intraportal islet allografts in type-1, insulin-dependent diabetic-patients. *Transplantation* 1991; 51(1):76-85	Observational study	236	9	167
40	Van der Laan LJW, et al. Infection by porcine endogenous retrovirus after islet xenotransplantation in scid mice. *Nature* 2000; 407(6800):90-94	Basic science	234	14	304
41	Webster KE, et al. In vivo expansion of t reg cells with IL-2-mab complexes: induction of resistance to eae and long-term acceptance of islet allografts without immunosuppression. *Journal of Experimental Medicine* 2009; 206(4):751-760	Basic science	233	29	242
42	Biarnes M, et al. Beta-cell death and mass in syngeneically transplanted islets exposed to short- and long-term hyperglycemia. *Diabetes* 2002; 51(1):66-72	Basic science	233	16	256
43	Hering BJ, et al. Transplantation of cultured islets from two-layer preserved pancreases in type 1 diabetes with anti-CD3 antibody. *American Journal of Transplantation* 2004; 4(3):390-401	Observational study	232	18	266
44	Oshea GM, et al. Prolonged survival of transplanted islets of Langerhans encapsulated in a biocompatible membrane. *Biochimica Et Biophysica Acta* 1984; 804(1):133-136	Basic science	231	7	202
45	Froud T, et al. Islet transplantation in type 1 diabetes mellitus using cultured islets and steroid-free immunosuppression: Miami experience. *American Journal of Transplantation* 2005; 5(8):2037-2046	RCT	229	19	249
46	Wang T, et al. An encapsulation system for the immunoisolation of pancreatic islets. *Nature Biotechnology* 1997; 15(4):358-362	Basic science	226	11	245
47	Warnock GL, et al. Long-term follow-up after transplantation of insulin-producing pancreatic-islets into patients with type-1 (insulin-dependent) diabetes-mellitus. *Diabetologia* 1992; 35(1):89-95	Observational study	224	9	178
48	Korbutt GS, et al. Large scale isolation, growth, and function of porcine neonatal islet cells. *Journal of Clinical Investigation*. 1996; 97(9):2119-2129.	Basic science	223	11	239
49	Ricordi C, et al. Human islet isolation and allotransplantation in 22 consecutive cases. *Transplantation.* 1992; 53(2):407-414.	Observational study	221	9	180
50	Warnock GL, et al. Normoglycemia after transplantation of freshly isolated and cryopreserved pancreatic-islets in type-1 (insulin-dependent) diabetes-mellitus. *Diabetologia* 1991; 34(1):55-58	Observational study	212	8	160

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Table 1

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Rank	Article	Study design	Citations in SCIE	Citations per year	Citations in SCOPUS
51	Linetsky E, et al. Improved human islet isolation using a new enzyme blend, liberase. *Diabetes* 1997; 46(7):1120-1123	Basic science	210	11	236
52	Carlsson PO, et al. Markedly decreased oxygen tension in transplanted rat pancreatic islets irrespective of the implantation site. *Diabetes* 2001; 50(3):489-495	Basic science	209	13	217
53	Lau H, et al. Prolongation of rat islet allograft survival by direct ultraviolet-irradiation of the graft. *Science* 1984; 223(4636):607-609	Basic science	209	6	129
54	Tian JD, et al. Modulating autoimmune responses to gad inhibits disease progression and prolongs islet graft survival in diabetes-prone mice. *Nature Medicine* 1996; 2 (12):1348-1353	Basic science	205	10	221
55	Shizuru JA, et al. Islet allograft survival after a single course of treatment of recipient with antibody to L3T4. *Science* 1987; 237(4812):278-280	Basic science	203	7	153
56	Oshea GM, et al. Encapsulation of rat islets of Langerhans prolongs xenograft survival in diabetic mice. *Diabetes* 1986; 35(8):943-946	Basic science	200	6	187
57	Levisetti MG, et al. Immunosuppressive effects of human CTLA4IG in a non-human primate model of allogeneic pancreatic islet transplantation. *Journal of Immunology* 1997; 159(11):5187-5191	Basic science	198	10	214
58	Mauer SM, et al. Pancreatic-islet transplantation - effects on glomerular lesions of experimental diabetes in rat. *Diabetes* 1974; 23(9):748-753	Basic science	196	5	107
59	Fan MY, et al. Reversal of diabetes in bb rats by transplantation of encapsulated pancreatic-islets. *Diabetes* 1990; 39(4):519-522	Basic science	191	7	179
60	Pileggi A, et al. Heme oxygenase-1 induction in islet cells results in protection from apoptosis and improved in vivo function after Transplantation. *Diabetes* 2001; 50 (9):1983-1991	Basic science	187	12	197
61	Johansson H, et al. Tissue factor produced by the endocrine cells of the islets of Langerhans is associated with a negative outcome of clinical islet Transplantation. *Diabetes* 2005; 54(6):1755-1762	Basic science	186	16	203
62	Piemonti L, et al. Human pancreatic islets produce and secrete MCP-1/CCL2: relevance in human islet Transplantation. *Diabetes* 2002; 51(1):55-65	Basic science	185	12	194
63	Cruise GM, et al. In vitro and in vivo performance of porcine islets encapsulated in interfacially photopolymerized poly(ethylene glycol) diacrylate membranes. *Cell Transplantation* 1999; 8(3):293-306	Basic science	185	10	203
64	Kaufman DB, et al. Differential roles of Mac-1+ cells, and CD4+ and CD8+ lymphocytes-t in primary nonfunction and classic rejection of islet allografts. *Journal of Experimental Medicine* 1990; 172(1):291-302	Basic science	182	7	156
65	Alejandro R, et al. Natural-history of intrahepatic canine islet cell autografts. *Journal of Clinical Investigation* 1986; 78(5):1339-1348	Basic science	179	6	132
66	Korbutt GS, et al. Cotransplantation of allogeneic islets with allogeneic testicular cell aggregates allows long-term graft survival without systemic immunosuppression. *Diabetes* 1997; 46(2):317-322	Basic science	178	9	187
67	Lakey JRT, et al. Variables in organ donors that affect the recovery of human islets of Langerhans. *Transplantation* 1996; 61(7):1047-1053	Basic science	178	8	209
68	Gores PF, et al. Insulin independence in type-i diabetes after transplantation of unpurified islets from single donor with 15-deoxyspergualin. *Lancet* 1993; 341 (8836):19-21	Observational study	178	7	145
69	Evgenov NV, et al. In vivo imaging of islet Transplantation. *Nature Medicine* 2006; 12 (1):144-148	Basic science	177	16	190
70	Deng SP, et al. Structural and functional abnormalities in the islets isolated from type 2 diabetic subjects. *Diabetes* 2004; 53(3):624-632	Basic science	177	14	200
71	Steiger J, et al. Il-2 knockout recipient mice reject islet-cell allografts. *Journal of Immunology* 1995; 155(1):489-498	Basic science	177	8	174
72	Soonshiong P, et al. Long-term reversal of diabetes by the injection of immunoprotected islets. *Proceedings of The National Academy of Sciences (PNAS)* 1993; 90(12):5843-5847	Basic science	177	7	185
73	Montana E, et al. Beta-cell mass and growth after syngeneic islet cell transplantation in normal and streptozocin diabetic C57BL/6 mice. *Journal of Clinical Investigation* 1993; 91(3):780-787	Basic science	175	7	160
74	Wang RN, et al. Maintenance of beta-cell function and survival following islet isolation requires re-establishment of the islet-matrix relationship. *Journal of Endocrinology* 1999; 163(2):181-190	Basic science	172	10	190
75	Noguchi H, et al. A new cell-permeable peptide allows successful allogeneic islet transplantation in mice. *Nature Medicine* 2004; 10(3):305-309	Basic science	171	13	187

(*continued*)

Table 1
(continued).

Rank	Article	Study design	Citations in SCIE	Citations per year	Citations in SCOPUS
76	Devos P, et al. Improved biocompatibility but limited graft survival after purification of alginate for microencapsulation of pancreatic islets. *Diabetologia* 1997; 40(3):262-270	Basic science	170	9	199
77	Najarian JS, et al. Human islet transplantation: preliminary-report. *Transplantation Proceedings* 1977; 9(1):233-236	Observational study	169	4	139
78	Elliott RBdsxw, et al. Live encapsulated porcine islets from a type 1 diabetic patient 9.5 yr after xenotransplantation. *Xenotransplantation* 2007; 14(2):157-161	Observational study	168	17	204
79	Toso C, et al. Clinical magnetic resonance imaging of pancreatic islet grafts after iron nanoparticle labeling. *American Journal of Transplantation* 2008; 8(3):701-706	Observational study	166	18	177
80	Sullivan SJ, et al. Biohybrid artificial pancreas - long-term implantation studies in diabetic, pancreatectomized dogs. *Science* 1991; 252(5006):718-721	Basic science	165	6	159
81	Bottino R, et al. Response of human islets to isolation stress and the effect of antioxidant treatment. *Diabetes* 2004; 53(10):2559-2568	Basic science	163	13	169
82	Bottino R, et al. Transplantation of allogeneic islets of Langerhans in the rat liver: effects of macrophage depletion of graft survival and microenvironment activation. *Diabetes* 1998; 47(3):316-323	Basic science	162	9	164
83	Barshes NR, et al. Inflammation-mediated dysfunction and apoptosis in pancreatic islet transplantation: implications for intrahepatic grafts. *Journal of Leukocyte Biology* 2005; 77(5):587-597	Review	161	13	170
84	Wang Y. The role of CD4+ and CD8+ T-cells in the destruction of islet grafts by spontaneously diabetic mice. *Proceedings of The National Academy of Sciences (PNAS)* 1991; 88(2):527-531	Basic science	160	6	124
85	Kenyon NS, et al. Long-term survival and function of intrahepatic islet allografts in baboons treated with humanized anti-CD154. *Diabetes* 1999; 48(7):1473-1481	Basic science	158	9	164
86	Rastellini C, et al. Granulocyte macrophage colony-stimulating factor-stimulated hepatic dendritic cell progenitors prolong pancreatic islet allograft survival. *Transplantation* 1995; 60(11):1366-1370	Basic science	156	7	156
87	Ozmen L, et al. Inhibition of thrombin abrogates the instant blood-mediated inflammatory reaction triggered by isolated human islets: possible application of the thrombin inhibitor melagatran in clinical islet Transplantation. *Diabetes* 2002; 51 (6):1779-1784	basic science	154	10	170
88	De Vos P, et al. Considerations for successful transplantation of encapsulated pancreatic islets. *Diabetologia* 2002; 45(2):159-173	Review	154	10	172
89	Soonshiong P, et al. Successful reversal of spontaneous diabetes in dogs by intraperitoneal microencapsulated islets. *Transplantation* 1992; 54(5):769-774	Basic science	153	6	156
90	Menger MD, et al. Angiogenesis and hemodynamics of microvasculature of transplanted islets of Langerhans. *Diabetes* 1989; 38():199-201	Basic science	153	5	142
91	Sutherland DER. Pancreas and islet transplantation .2. clinical-trials. *Diabetologia* 1981; 20(4):435-450	Review	153	4	91
92	Wahoff DC, et al. Autologous islet transplantation to prevent diabetes after pancreatic resection. *Annals of Surgery* 1995; 222(4):562-579	Observational study	152	7	172
93	Duvivier-Kali VF, et al. Complete protection of islets against allorejection and autoimmunity by a simple barium-alginate membrane. *Diabetes* 2001; 50(8):1698-1705	Basic science	151	9	184
94	Zhang N, et al. Elevated vascular endothelial growth factor production in islets improves islet graft vascularization. *Diabetes.* 2004; 53(4):963-970.	basic science	150	12	160
95	Alexander AM, et al. Indoleamine 2,3-dioxygenase expression in trans-planted nod islets prolongs graft survival after adoptive transfer of diabetogenic splenocytes. *Diabetes* 2002; 51(2):356-365	Basic science	150	10	163
96	Zheng XX, et al. Administration of noncytolytic IL-10/FC in murine models of lipopolysaccharide-induced septic shock and allogeneic islet transplantation. *Journal of Immunology* 1995; 154(10):5590-5600	Basic science	150	7	154
97	Ryan EA, et al. Assessment of the severity of hypoglycemia and glycemic lability in type 1 diabetic subjects undergoing islet Transplantation. *Diabetes* 2004; 53(4):955-962	Observational study	149	11	198
98	Steffes MW, et al. Amelioration of mesangial volume and surface alterations following islet transplantation in diabetic rats. *Diabetes* 1980; 29(7):509-515	Basic science	149	4	76
99	Griffith RC, et al. Morphologic study of intrahepatic portal-vein islet isografts. *Diabetes.* 1977; 26(3):201-214.	Basic science	149	4	93
100	Jansson L, et al. Graft vascular function after transplantation of pancreatic islets. *Diabetologia* 2002; 45(6):749-763	Review	146	10	165

(*continued*)

Table 1
(continued).

Rank	Article	Study design	Citations in SCIE	Citations per year	Citations in SCOPUS
101	Bennet W, et al. Damage to porcine islets of Langerhans after exposure to human blood in vitro, or after intraportal transplantation to cynomologus monkeys: protective effects of SCR1 and heparin. *Transplantation* 2000; 69(5):711-719	Basic science	146	9	156
102	Lakey JRT, et al. Intraductal collagenase delivery into the human pancreas using syringe loading or controlled perfusion. *Cell Transplantation* 1999; 8(3):285-292	Basic science	146	8	165

RCT = randomized controlled trial.

1990. Figure 1B summarizes the study design of the top-cited articles. Most of these articles were in basic science (n = 75), whereas the remaining articles were observational studies (n = 21), reviews (n = 5), and RCTs (n = 1). No articles involved guidelines or meta-analyses.

Oxford Centre for Evidence-based Medicine—Levels of Evidence (2009 edition) was used to evaluate all studies. There was only 1 study at levels 1c, and 21 and 80 studies at levels 4 and 5, respectively.

3.3. Authors, countries, and institutions

We carefully analyzed the distribution of primary authors of top-cited articles. Fifteen of the authors had published more than 1 article, as shown in Table 3. Ryan et al published the most (n = 4), followed by Hering et al and Soonshiong et al (n = 3).

The top-cited articles originated from 18 countries (Fig. 2). The countries producing the most articles were the USA (n = 70), followed by Canada (n = 20), Sweden (n = 9), and Italy (n = 7). Only 23 articles were written by multinational collaborations; 79 articles were authored by researchers from the same country.

Sixteen institutions published 3 or more of the 100 most frequently cited articles (Table 4). Ten (62.5%) of these institutions were located in the US. Of the 8 (37.5%) institutions outside the US, 4 were in Canada (n = 2) and Sweden (n = 2), and 2 were in Italy (n = 1) and Switzerland (n = 1). The institutions producing the most articles were the University of Alberta (n = 15), followed by the University of Minnesota (n = 14), Harvard University (n = 13), the University of Washington (n = 12), and the University of Miami (n = 11).

3.4. Journals

We found that the top-cited articles were published in 25 journals (Table 5). More than half (52%, n = 53) of the articles were published in journals that specialized in the fields of diabetes mellitus or transplantation; the largest number (n = 30) of articles was published in *Diabetes*. The remaining articles were published in less specialized journals; in particular, 2 general high-impact factor journals (*Proceedings of the National Academy of Sciences* [PNAS] and *Science*) published 9 and 8 articles, respectively (ranks 2 and 3). No correlations were found between the impact factors of the journals and the number of top-cited articles they published when the articles were stratified into 3 groups: a low impact factor (IF) group (0–4.9), a middle IF group (5–9.9), and a high IF group (≥10); the impact factors were, respectively, $r = 0.11$, $P = .79$; $r = 0.37$, $P = .42$; $r = -0.26$, and $P = .46$.

3.5. Investigation of possible factors influencing citations

To identify the factors that determined the number of citations of top-cited articles, we investigated possible correlations between the number of citations and the number of authors, institutions, years since publication, and countries involved. No correlations were found between the number of citations and years since publication ($r = 0.02$, $P = .79$), authors ($r = 0.13$,

Table 2
High-frequency references in the top-cited articles.

Rank	Article	Frequency	Order in the top 100 articles
1	Shapiro AMJ, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. *New England Journal of Medicine* 2000; 343(4):230-238	23	1
2	Ricordi C, et al. Automated method for isolation of human pancreatic islets. *Diabetes* 1988;37(4):413-20	22	NA
3	Lacy PE, Kostianovsky M. Method for the isolation of intact islets of Langerhans from the rat pancreas. *Diabetes* 1967;16(1):35-39	17	NA
4	Ricordi C, et al. Islet isolation assessment in man and large animals. *Acta Diabetol Lat* 1990;27(3):185-195	14	NA
5	Scharp DW, et al. Insulin independence after islet transplantation into type-I diabetic patient. *Diabetes* 1990; 39 (4):515-518	13	28
6	Ryan EA, et al. Clinical outcomes and insulin secretion after islet transplantation with the Edmonton protocol. *Diabetes* 2001; 50(4):710-719	12	7
7	Lakey JRT, et al. Intraductal collagenase delivery into the human pancreas using syringe loading or controlled perfusion. *Cell Transplantation* 1999; 8(3):285-292	11	102
8	Lim F, Sun AM. Microencapsulated islets as bioartificial endocrine pancreas. *Science* 1980; 210(4472):908-910	11	NA
9	Tzakis AG, et al. Pancreatic-islet transplantation after upper abdominal exenteration and liver replacement. *Lancet* 1990; 336(8712):402-405	10	38

NA = Not Applicable (no records in the top 100 articles).

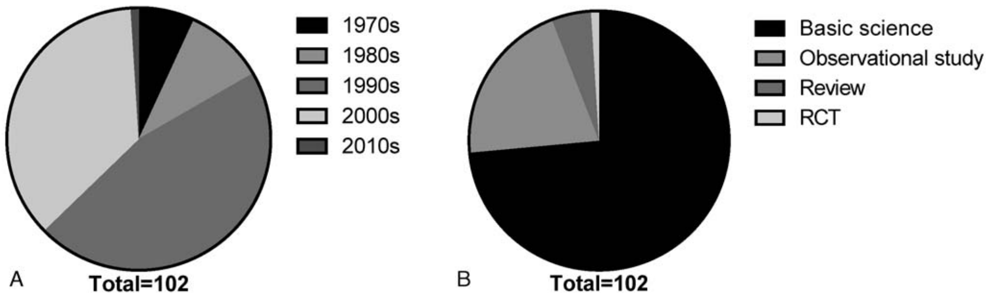

Figure 1. Distribution of top-cited articles in the field of islet transplantation. (A) Time distribution by decade. The results show that the largest cluster of articles (47) was published during the 1990s. (B) Type distribution by study design. Observational studies predominated among top-cited articles.

$P=.18$), institutions ($r=0.08$, $P=.41$), or countries involved ($r=0.02$, $P=.85$) (Fig. 3).

3.6. Keyword analysis

To assess the historical development of islet transplantation research and current trends, we analyzed variations in keywords from different periods. Overall, the most frequently used keywords were insulin dependence, insulin secretion, immunosuppression, encapsulation, rejection and survival. Keywords such as "insulin secretion" and "immunosuppression" increased in frequency between the 1970s and the 2000/10s, whereas keywords such as insulin dependence, rejection, survival, and encapsulation peaked during the 1990s. Only 1 article was from 2010, and so results from that decade were integrated into the 2000s (Fig. 4). Graft types were also top-listed keywords. The 100 most frequently cited articles were divided into 4 groups: allografts, autografts, isografts, and xenografts. In all decades, the allograft was the most common type of graft (76%), followed by the xenograft (16%); isografts and autografts were scare (Fig. 5).

3.7. Citation network

Citation network analysis was carried out to reveal the citation links and research topics of the 100 most frequently cited articles. Three close citation networks (3 clusters) were identified through a CitNetExplorer cluster analysis, as can be seen in Fig. 6. Three citation networks were rooted in 3 classical publications (Kemp CB, 1973; Ballinger WF, 1972; Griffith RC, 1977); we have therefore referred to them as the Kemp-cluster, the Ballinger-cluster, and the Griffith-cluster (Fig. 6). Publications included in the Kemp-cluster discussed the use of antirejection immunotherapies or biocompatible encapsulations to prolong graft survival. Publications included in the Ballinger-cluster tended to focus on assessing the efficacy (measured through insulin secretions and independence) of islet transplants. Publications in the Griffith-cluster discussed the structure and function of isolated or transplanted islets.

Table 3

Primary authors of top-cited articles on islet transplantation.

Authors	Number of articles
Ryan EA	4
Hering BJ	3
Soonshiong P	3
Bennet W	2
Bottino R	2
De Vos P	2
Kenyon NS	2
Korbutt GS	2
Lacy PE	2
Lakey JRT	2
Mauer SM	2
Oshea GM	2
Scharp DW	2
Shapiro AMJ	2
Warnock GI	2

4. Discussion

In this study, we used bibliometric analysis to identify and characterize the 100 most frequently cited articles in the field of islet transplantation. The top-cited articles on islet transplantation were cited 146 to 2988 times. This number is much lower than the equivalent in some other medical fields, such as hypertension (582–7248) and diabetes (1121–10292), but higher than orthodontics (89–545) and orthopedic elbow surgery (124–388), to name only a few.[12,14,15,25] Citations differed between specialties, mainly depending on the number of researchers in specific medical fields.[26] Open access may be another important factor in attracting citations. Open-access (OA) articles are more easily recognized and cited than non-OA articles. [27] Further analysis has shown that, for the same author, publications in OA journals have a higher rate of citation than publications in traditional, non-OA journals in some medical fields, such as cytopathology. [28] However, OA articles have not received significantly more citations than non-OA articles in dentistry and ophthalmology. [29,30] It is therefore clear that the extent to which OA increases citations varies across different research fields.

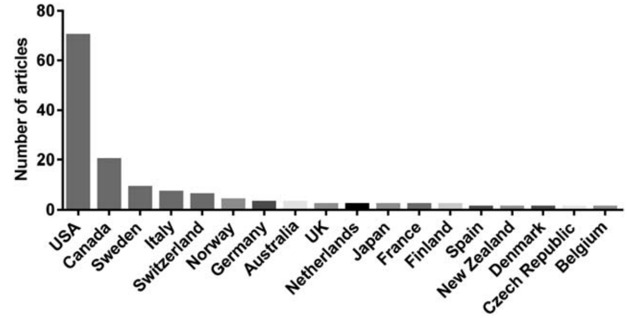

Figure 2. Countries of origin of top-cited articles in the field of islet transplantation.

Table 4

Institutions of origin with three or more top-cited articles in islet transplantation.

Institution	Number of articles	Country
University of Alberta	15	Canada
University of Minnesota	14	USA
Harvard University	13	USA
University of Miami	11	USA
University of Washington	11	USA
Uppsala University	9	Sweden
University of California	7	USA
University of Pittsburgh	5	USA
San Raffaele University	4	Italy
University of Chicago	4	USA
University of Pennsylvania	4	USA
Scripps Research Institute	3	USA
University of Colorado	3	USA
University of Geneva	3	Switzerland
University of Kalmar	3	Sweden
University of Toronto	3	Canada

Table 5

Journals publishing top-cited articles.

Journals	Number of articles	Impact factor (2016)
Diabetes	30	8.784
Proceedings of the National Academy of Sciences (PNAS)	9	9.423
Science	8	34.661
Diabetologia	7	6.206
Nature Medicine	6	30.357
Transplantation	6	3.690
Journal of Clinical Investigation	5	12.575
Lancet	5	44.002
Journal of Immunology	4	4.985
American Journal of Transplantation	3	5.669
New England Journal of Medicine	3	59.558
Cell Transplantation	2	3.427
Journal of Experimental Medicine	2	11.240
Annals of Surgery	1	8.569
Biochimica et Biophysica Acta	1	5.128
Diabetes Care	1	8.934
Endocrinology	1	4.159
JAMA	1	37.684
Journal of Endocrinology	1	4.498
Journal of Leukocyte Biology	1	4.165
Nature	1	38.138
Nature Biotechnology	1	43.113
Surgery	1	3.309
Transplantation Proceedings	1	0.867
Xenotransplantation	1	3.789

The decade during which most top-cited articles in the field of islet transplantation were published was the 1990s. In all, 85 articles (83%) were published after 1990. This result suggests that it may take 15 years or more for article citations to peak, as documented through bibliometric analysis.[25,31] There are several reasons for this finding. First, more articles on islet transplantation have emerged in the past 15 years, and researchers tend to cite the most recent study. In addition, Ricordi et al's[32] discovery of an automated method for isolating islets from the human pancreas in 1989 greatly stimulated subsequent research into islet transplantation.

We have demonstrated that basic science is the most frequent type of study design. This trend runs counter to many medical specialties, in which most articles are observational studies.[12,14,25,33] There is only 1 randomized clinical trial (level 1c) of islet transplantation; thus more high-level evidence of clinical trials were needed in the future research. Although the demand for islet transplantation among diabetic patients far exceeds the number of islets available, there are too few human

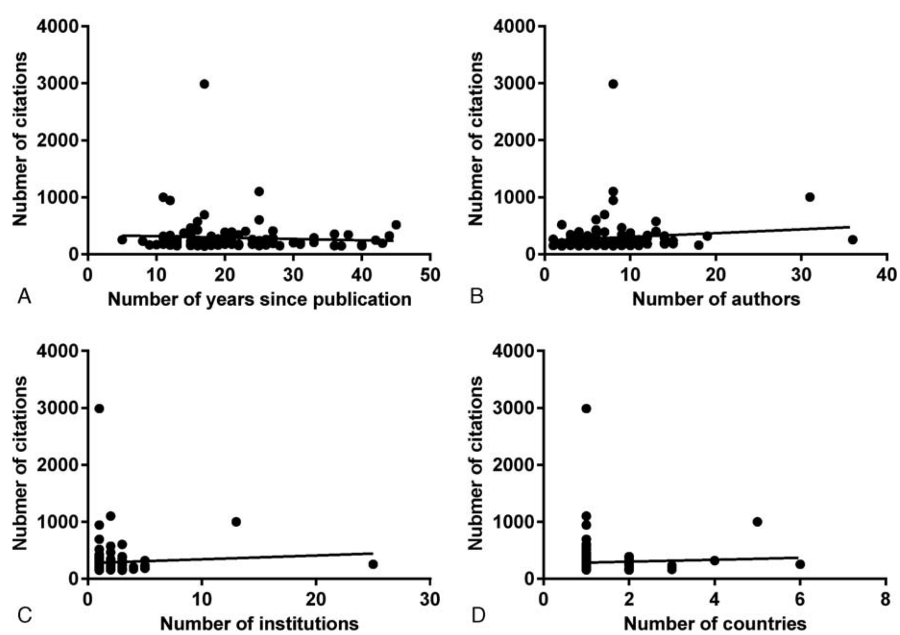

Figure 3. Correlations between the number of citations and the number of years since publication (A); the number of authors (B); the number of institutions (C); and the number of countries involved (D).

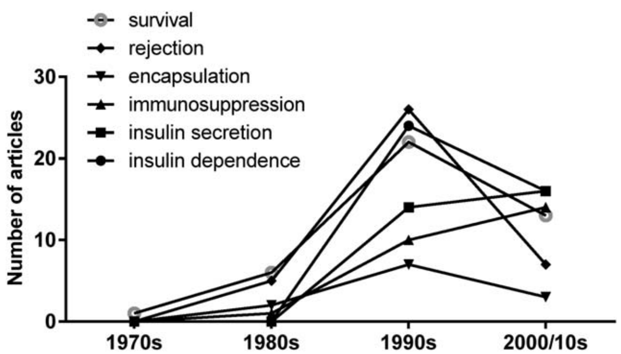

Figure 4. Trends over time: common keywords found in the 100 most frequently cited articles. 2000/2010: Only 1 article was written in the 2010; for this reason, the results from this decade were integrated into the 2000s.

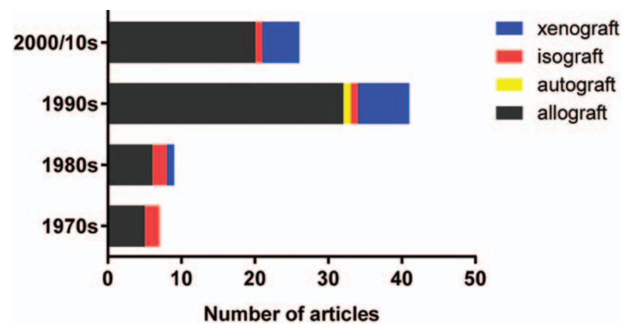

Figure 5. Time trends in the distribution of the 100 most frequently cited articles by graft type. 2000s/2010s: Only 1 article was written in the 2010; for this reason, the results from this decade were integrated into the 2000.

pancreatic islets to meet the need for transplantation. Thus, the pressure to create an ample supply of islets has led to extensive basic-science research, including xenografts of porcine islets.[4]

Our study found that most top-cited articles were written in the US; 10 (62.5%) of the 16 top centers for islet transplantation are also located in the US. These results are in line with the origin of the 100 most frequently cited articles in many other medical fields.[8,11,34] The US leads the world in medical research, given its large number of researchers and generous research funding. In addition, American authors tend to cite local articles and US reviewers prefer American articles.[31,35,36]

The 100 most frequently cited articles were published in 25 journals. Because the clinical application of islet transplantation is to treat diabetes mellitus, it is not surprising that more than half of the articles were published in journals specializing in the fields of diabetes mellitus or transplantation. As indicated by Bradford's law, a few core journals in the specialized field were mainly used to obtain citations; there were significantly fewer citations of articles published in non-core journals.[37] Thus, most of top-cited articles appeared in a few major, specialized medical journals. In this case, the specialized journal *Diabetes* published the most articles (n=30). However, many top-cited articles on islet transplantation were published in high impact factor general medical journals, such as *PNAS* (n=9) and *Science* (n=9).

Previous studies have shown that the impact factor of particular journals is the best indicator for citations; top-cited articles usually appeared in journals with high impact factors.[38] Our study does not support this finding. Our results suggest that citations were not clearly influenced by the impact factor of the journals, as other reports have also shown.[12] Perhaps, the tendency for top-cited articles to be published in general or specialized journals varies across different medical fields. Top-cited articles on hypertension and tuberculosis, for example, tend

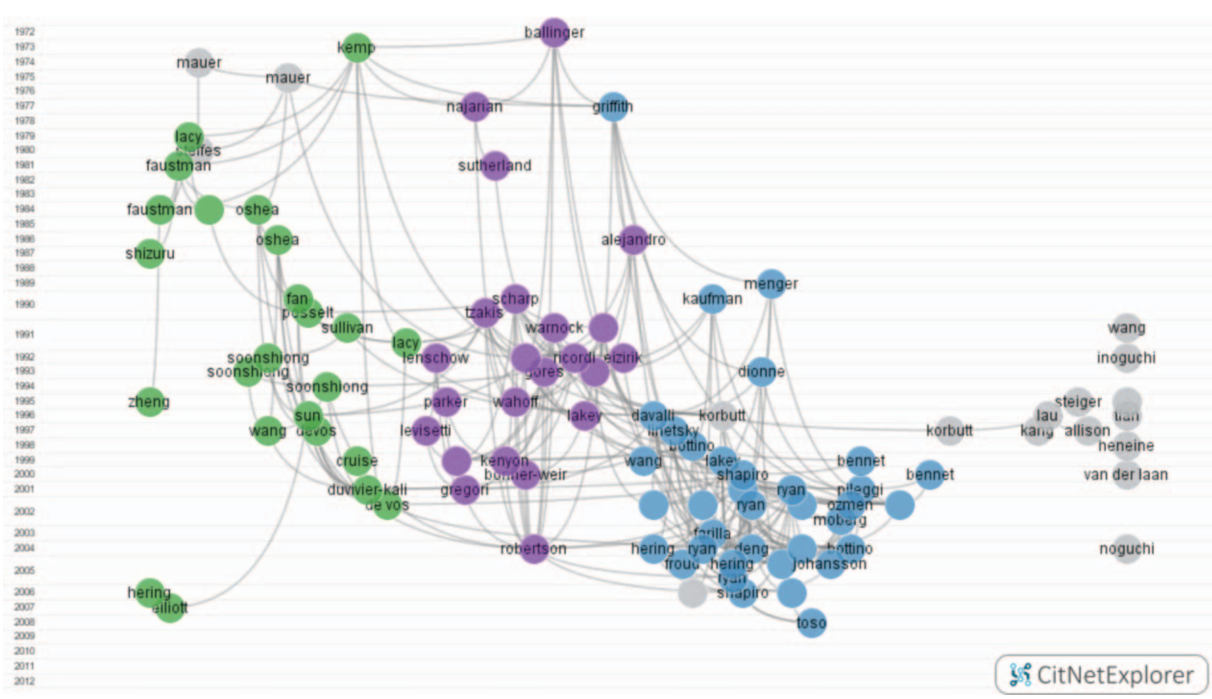

Figure 6. Citation networks visualizing the research topics of the 100 most frequently cited articles. Kemp-cluster: green; Ballinger-cluster: purple; Griffith-cluster: blue.

to be published in general journals, whereas those on lung transplantation are usually published in specialized journals.[14,18,39] These findings suggest the need to develop measures to assess the significance of specific research papers that are more accurate.

Our study found a correlation between a high number of allografts and highly rated examples of islet transplantation, mainly because pancreatic islets are more readily available for allografts than for isografts or autografts. In addition, pancreatic islet allografts carried out using the Edmonton protocol result in successful insulin independence and glycemic control in type 1 diabetic patients.[24] However, the clinical outcome of allogeneic islet transplantation is mainly complicated by graft rejection. An analysis of keywords and citation networks shows that many of the 100 most frequently cited articles discuss ways to prolong graft survival through antirejection immunotherapies or biocompatible encapsulations. It is postulated that, in future, research will focus on autografts that are not susceptible to immune rejection. Furthermore, the demand for islet transplantation will expand in patients with type 1 diabetes mellitus, causing the current supply of islets derived from human organ donors to fail to meet demand. Perhaps, porcine sources can provide sufficient islets to meet clinical demand, increasing xenograft research.

This study has some limitations. First, we have only used a single medical database, the SCIE, for our analysis. It is worth noting that the SCIE does not index all journals; as a result, some journals indexed by the Google Scholar or SCOPUS databases may have been missed. Although different databases return vastly different results,[40,41] it is acceptable to use a single medical database to identify top-cited medical research articles—many published bibliometric analyses have used the SCIE database for this purpose. [14,20,42] Another potential source of bias involves the "obliteration by incorporation" effect described by Garfield et al, which has been demonstrated in the literature of other medical fields. [43,44] This effect refers to the phenomenon by which older classic articles gradually lose the spotlight position, and are no longer cited with the same frequency because their findings have been incorporated into the current knowledge of the field. To counter this effect, we used the total number of citations received, rather than the number of citations received during the current year to generate our list of top-cited articles. Using current-year citations as screening criteria would have caused an unfair relative increase in citations for more recent articles, overlooking many older classic articles. Using the total number of citations ensures that older articles, which have accumulated many citations over time, warrant inclusion.[25] Other potential factors that affect citations cannot be accurately determined; these include journal and author self-citations; citations in textbooks, conferences, and web-based literatures; and omission bias.[31,45] Such biases may affect the generation of a representative list of top-cited articles based on absolute citation counts.

5. Conclusions

Despite these limitations, this study successfully reveals the characteristics of top-cited articles in the field of islet transplantation. Most involve basic science, have been published in *Diabetes*, and originate from institutions in the US. Following on from clinically successful allografts using the Edmonton protocol, autografts and xenografts should be strengthened to solve the problems of immune rejection and islet sources, respectively.

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