

World Journal of *Clinical Cases*

World J Clin Cases 2021 June 6; 9(16): 3796-4115



REVIEW

- 3796** COVID-19 and the digestive system: A comprehensive review
Wang MK, Yue HY, Cai J, Zhai YJ, Peng JH, Hui JF, Hou DY, Li WP, Yang JS

MINIREVIEWS

- 3814** COVID-19 impact on the liver
Baroiu L, Dumitru C, Iancu A, Leşe AC, Drăgănescu M, Baroiu N, Anghel L
- 3826** Xenogeneic stem cell transplantation: Research progress and clinical prospects
Jiang LL, Li H, Liu L

ORIGINAL ARTICLE

Case Control Study

- 3838** Histopathological classification and follow-up analysis of chronic atrophic gastritis
Wang YK, Shen L, Yun T, Yang BF, Zhu CY, Wang SN

Retrospective Study

- 3848** Effectiveness of sharp recanalization of superior vena cava-right atrium junction occlusion
Wu XW, Zhao XY, Li X, Li JX, Liu ZY, Huang Z, Zhang L, Sima CY, Huang Y, Chen L, Zhou S
- 3858** Management and outcomes of surgical patients with intestinal Behçet's disease and Crohn's disease in southwest China
Zeng L, Meng WJ, Wen ZH, Chen YL, Wang YF, Tang CW
- 3869** Clinical and radiological outcomes of dynamic cervical implant arthroplasty: A 5-year follow-up
Zou L, Rong X, Liu XJ, Liu H

Observational Study

- 3880** Differential analysis revealing APOC1 to be a diagnostic and prognostic marker for liver metastases of colorectal cancer
Shen HY, Wei FZ, Liu Q

Randomized Clinical Trial

- 3895** Comparison of white-light endoscopy, optical-enhanced and acetic-acid magnifying endoscopy for detecting gastric intestinal metaplasia: A randomized trial
Song YH, Xu LD, Xing MX, Li KK, Xiao XG, Zhang Y, Li L, Xiao YJ, Qu YL, Wu HL

CASE REPORT

- 3908** Snapping wrist due to bony prominence and tenosynovitis of the first extensor compartment: A case report
Hu CJ, Chow PC, Tzeng IS
- 3914** Massive retroperitoneal hematoma as an acute complication of retrograde intrarenal surgery: A case report
Choi T, Choi J, Min GE, Lee DG
- 3919** Internal fixation and unicompartmental knee arthroplasty for an elderly patient with patellar fracture and anteromedial osteoarthritis: A case report
Nan SK, Li HF, Zhang D, Lin JN, Hou LS
- 3927** Haemangiomas in the urinary bladder: Two case reports
Zhao GC, Ke CX
- 3936** Endoscopic diagnosis and treatment of an appendiceal mucocele: A case report
Wang TT, He JJ, Zhou PH, Chen WW, Chen CW, Liu J
- 3943** Diagnosis and spontaneous healing of asymptomatic renal allograft extra-renal pseudo-aneurysm: A case report
Xu RF, He EH, Yi ZX, Li L, Lin J, Qian LX
- 3951** Rehabilitation and pharmacotherapy of neuromyelitis optica spectrum disorder: A case report
Wang XJ, Xia P, Yang T, Cheng K, Chen AL, Li XP
- 3960** Undifferentiated intimal sarcoma of the pulmonary artery: A case report
Li X, Hong L, Huo XY
- 3966** Chest pain in a heart transplant recipient: A case report
Chen YJ, Tsai CS, Huang TW
- 3971** Successful management of therapy-refractory pseudoachalasia after Ivor Lewis esophagectomy by bypassing colonic pull-up: A case report
Flemming S, Lock JF, Hankir M, Reimer S, Petritsch B, Germer CT, Seyfried F
- 3979** Old unreduced obturator dislocation of the hip: A case report
Li WZ, Wang JJ, Ni JD, Song DY, Ding ML, Huang J, He GX
- 3988** Laterally spreading tumor-like primary rectal mucosa-associated lymphoid tissue lymphoma: A case report
Wei YL, Min CC, Ren LL, Xu S, Chen YQ, Zhang Q, Zhao WJ, Zhang CP, Yin XY
- 3996** Coronary artery aneurysm combined with myocardial bridge: A case report
Ye Z, Dong XF, Yan YM, Luo YK
- 4001** Thoracoscopic diagnosis of traumatic pericardial rupture with cardiac hernia: A case report
Wu YY, He ZL, Lu ZY

- 4007** Delayed diagnosis and comprehensive treatment of cutaneous tuberculosis: A case report
Gao LJ, Huang ZH, Jin QY, Zhang GY, Gao MX, Qian JY, Zhu SX, Yu Y
- 4016** Rapidly progressing primary pulmonary lymphoma masquerading as lung infectious disease: A case report and review of the literature
Jiang JH, Zhang CL, Wu QL, Liu YH, Wang XQ, Wang XL, Fang BM
- 4024** Asymptomatic carbon dioxide embolism during transoral vestibular thyroidectomy: A case report
Tang JX, Wang L, Nian WQ, Tang WY, Xiao JY, Tang XX, Liu HL
- 4032** Transient immune hepatitis as post-coronavirus disease complication: A case report
Drăgănescu AC, Săndulescu O, Bilașco A, Kouris C, Streinu-Cercel A, Luminos M, Streinu-Cercel A
- 4040** Acute inferior myocardial infarction in a young man with testicular seminoma: A case report
Scafa-Udriste A, Popa-Fotea NM, Bataila V, Calmac L, Dorobantu M
- 4046** Asymptomatic traumatic rupture of an intracranial dermoid cyst: A case report
Zhang MH, Feng Q, Zhu HL, Lu H, Ding ZX, Feng B
- 4052** Parotid mammary analogue secretory carcinoma: A case report and review of literature
Min FH, Li J, Tao BQ, Liu HM, Yang ZJ, Chang L, Li YY, Liu YK, Qin YW, Liu WW
- 4062** Liver injury associated with the use of selective androgen receptor modulators and post-cycle therapy: Two case reports and literature review
Koller T, Vrbova P, Meciarova I, Molcan P, Smitka M, Adamcova Selcanova S, Skladany L
- 4072** Spinal epidural abscess due to coinfection of bacteria and tuberculosis: A case report
Kim C, Lee S, Kim J
- 4081** Rare complication of inflammatory bowel disease-like colitis from glycogen storage disease type 1b and its surgical management: A case report
Lui FCW, Lo OSH
- 4090** Thymosin as a possible therapeutic drug for COVID-19: A case report
Zheng QN, Xu MY, Gan FM, Ye SS, Zhao H
- 4095** Arrhythmogenic right ventricular cardiomyopathy characterized by recurrent syncope during exercise: A case report
Wu HY, Cao YW, Gao TJ, Fu JL, Liang L
- 4104** Delayed pseudoaneurysm formation of the carotid artery following the oral cavity injury in a child: A case report
Chung BH, Lee MR, Yang JD, Yu HC, Hong YT, Hwang HP
- 4110** Atezolizumab-induced anaphylactic shock in a patient with hepatocellular carcinoma undergoing immunotherapy: A case report
Bian LF, Zheng C, Shi XL

ABOUT COVER

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Xenogeneic stem cell transplantation: Research progress and clinical prospects

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Abstract

Organ transplantation is the ultimate treatment for end-stage diseases such as heart and liver failure. However, the severe shortage of donor organs has limited the organ transplantation progress. Xenogeneic stem cell transplantation provides a new strategy to solve this problem. Researchers have shown that xenogeneic stem cell transplantation has significant therapeutic effects and broad application prospects in treating liver failure, myocardial infarction, advanced type 1 diabetes mellitus, myelosuppression, and other end-stage diseases by replacing the dysfunctional cells directly or improving the endogenous regenerative milieu. In this review, the sources, problems and solutions, and potential clinical applications of xenogeneic stem cell transplantation will be discussed.

Key Words: Xenogeneic stem cells; Transplantation; Immune rejection; Organ reconstruction; Neurological diseases; Tissue defects

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Core Tip: The severe shortage of donor organs generates long waiting lists for patients with end-stage diseases anticipating organ transplantation and ultimately leads to the deaths for those who are not fortunate to receive an organ. Xenogeneic stem cell transplantation provides a new strategy to solve this problem. In this review, we summarize possible problems and solutions and the clinical prospects of xenogeneic stem cell transplantation.

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INTRODUCTION

Organ transplantation is the ultimate treatment for end-stage diseases, such as liver failure, myocardial infarction, and advanced type 1 diabetes mellitus. The demand for organ transplants has been increasing for decades all around the world. Thus, the severe shortage of donor organs has become the biggest obstacle to organ transplantation[1-3]. In 2017, there were 114000 patients in the United States on waiting lists for organ transplantations. On average, 20 of these patients die every day because of their inability to obtain a suitable organ[4]. Moreover, organ shortage is more serious in some regions outside the United States. For example, in less developed regions, the success rate of transplantations decreased owing to the inconvenient transportation processes of transplanted organs. In addition, organ donation is opposed by some religious groups. Timely organ harvesting and transplantation are also influenced by controversial standards of death set by different religions[5,6].

Owing to the aforementioned limitations of organ transplantation, an alternative strategy for end-stage diseases is urgently needed. Thus, some researchers have focused on stem cell transplantation, which has achieved progress in the treatment of many diseases. For example, the induction of human embryonic stem cells (ESCs) into hepatocytes is an option for cell replacement therapy in liver diseases[7]. Hematopoietic stem cell transplantation is gradually becoming a mature therapy for a variety of hematologic malignancies[8]. These researchers have shown that stem cell transplantation is the most promising alternative treatment for end-stage diseases. However, with the development of allogeneic stem cell transplantation, it has been found that human stem cells are restricted in large-scale clinical applications for the following reasons. First, the human stem cell source is still limited because the number of stem cells in the human body decreases considerably with aging. Second, isolation of human stem cells is an invasive operation associated with specific ethical issues. Third, the prolonged time period needed to isolate and culture primary human stem cells makes them inconvenient for use in large-scale clinical applications. Fourth, relatively expensive and complex operations restrict the large-scale commercial production and application of human stem cells. Finally, it is difficult to perform quality control on human compared with animal stem cells[2,9,10]. Therefore, more researchers have been focused on the identification of alternative xenogeneic approaches with stem cells from animals for transplantation.

With the continuous development of xenogeneic stem cell transplantation, numerous researchers have demonstrated that it has considerable therapeutic effects and broad application prospects in treating liver failure, myocardial infarction, advanced type 1 diabetes mellitus, myelosuppression, and other end-stage diseases based (1) On the direct replacement of dysfunctional cells; or (2) On the improvement of the endogenous regenerative milieu[11-15]. Although potential problems in xenogeneic stem cell transplantation remain, many researchers have conducted numerous studies to solve these issues[3,16]. In this review, the sources, problems and solutions, and potential clinical applications of xenogeneic stem cell transplantation will be discussed.

SOURCES OF XENOGENEIC STEM CELLS

The sources of xenogeneic stem cells are extensive. Nonhuman primates, domestic animals, and rodents are promising cell sources for transplantation. Nonhuman primates that are genetically and physiologically close to humans are the leading cell sources[11,14,15]. Horn *et al*[14] injected baboon hematopoietic stem and progenitor cells in nonobese diabetic/severe combined immune-deficient mice. The results showed that CD34-enriched cells are capable for hematopoietic reconstitution[14]. However, many nonhuman primates are endangered species with limited access to stem cells. To guarantee cell sources, many researchers have turned their attention to domestic animals and rodents. Domestic animals include pigs, rabbits, dogs, cats, horses, sheep, goats, and cows, which are extensively recognized as suitable donors of xenogeneic stem cells owing to easy accessibility, breed capability, and low cost[17].

Among all domestic animals, most researchers have focused on pigs and porcine stem cells. Porcine stem cells are regarded as ideal candidates for cell transplantation owing to their comparatively larger sizes and accessibility[18-22]. Zhu *et al*[12] injected porcine adipose-derived stem cells (ADSCs) in the portal vein of acute-on-chronic liver failure rabbits, and showed that ADSCs migrated to the female rabbit liver and differentiated to hepatocytes[12]. Some researchers have paid attention to the rabbit for its docile character and high-reproductive rate. Li *et al*[9] has isolated umbilical cord mesenchymal stem cells (MSCs) from rabbits to repair murine bone defects by tissue engineering[9]. Considering the strong reproductive capacity, short reproductive cycle, and sufficient species-specific reagents of rodents[17], there is a possibility of using rodents as a xenogeneic stem cell transplantation source. Kasraeian *et al*[23] injected mouse bone marrow mesenchymal stem cells (BMSCs) into the liver of rat fetuses in utero on day 14 of pregnancy and the result showed that these cells were capable to remain functional probably as hepatocyte-like cells in the liver of infant rats[23]. Jia *et al* incubated rat ADSCs with normal human serum and the result showed that these cells can protect themselves from human xenoantibody and complement-mediated lysis[24]. These studies suggest that rodents might be one possible source of xenogeneic stem cells in the future, while there remains a long way to go before its clinical application.

Regarding the choice of accessible stem cell types, the most frequently used xenogeneic stem cells include MSCs, ESCs, induced pluripotent stem cells (iPSCs), and placenta-derived cells. MSCs have been regarded as the most ideal cell type on account of their extensive cell sources, lack of ethical restrictions for its use, easy accessibility without invasiveness, high survivability in *in vivo* conditions, low-immunological characteristics, low tumorigenicity, and high safety in clinical applications[18-22]. Many research studies have demonstrated that xenogeneic MSC transplantation is effective in the treatment of liver failure, myocardial infarction, and bone defects[9,12,13]. ESCs have also gained attention with their totipotency and high-self-renewal capacity[10].

PROBLEMS AND SOLUTIONS OF XENOGENEIC STEM CELL TRANSPLANTATION

Problems associated with xenogeneic stem cell transplantation, including immunological incompatibility, cell death, abnormal cell differentiation and proliferation, viral transmission from animals to humans, and ethical problems, hinder its clinical applications[3,16]. To solve these problems, numerous researchers have embarked on various studies that have led to great achievements.

Immune rejection

Immune rejection is undoubtedly the problem that generates considerable concern among all xenogeneic stem cell transplantation problems. Methods employed to suppress immune rejection include: (1) The choice of an appropriate stem cell type; (2) Gene editing technology; (3) Encapsulated cell technology; (4) Immunosuppressive drugs; (5) Regulation of cytokine levels; and (6) The use of cellular desensitization technology. These methods have helped enhance the transplantation success rate.

Choosing stem cells with low immunogenicity, immuno-suppressive and immune-modulatory properties could solve this problem. Ding *et al* transplanted human umbilical cord stroma-derived stem cells in immunocompetent mice. The results showed that this type of human stem cell has immunosuppressive and immunomodulatory properties[25]. Subsequently, a number of researchers showed that xenogeneic stem cells, especially xenogeneic MSCs, have low immunogenicity, and immunosuppressive and immune-modulatory properties[26-29]. Porcine MSCs have been favored in xenotransplantation studies owing to their low-immunogenicity properties and immunomodulatory features[19,24,27-29]. Yang *et al*[27] and Medicetty *et al*[28] transplanted porcine umbilical cord MSCs and porcine ESC-derived neuronal progenitors in non-immunocompromised rats separately. Their results yielded similar cell immunosuppressive effects[27,28]. Li *et al*[9] transplanted rabbit umbilical cord MSCs with hyaluronic acid/tricalcium phosphate scaffolds in rats and exhibited the low-immunogenicity properties and immune suppression capabilities of rabbit umbilical cord MSCs[9]. L  v  que *et al*[26] co-transplanted rat MSCs with porcine neuroblasts in immunocompetent rat striata, and demonstrated the immunosuppressive properties of these cells. Jia *et al*[24] demonstrated that rat ADSCs are capable of protecting themselves from human xenoantibodies and complement-mediated lysis,

which is dependent on CD59 and is correlated with low expression of galactose- α -1,3-galactose (α -Gal)[24]. All the aforementioned research studies suggest that the choices of the appropriate stem cell types can reduce immune rejection without other measures.

To further reduce the possibility of immune rejection, we discuss herein other methods for the suppression of immune rejection. Considering that stem cells are much easier to use for gene editing than organs, gene editing technology is the most promising approach, and has a major advantage in suppressing immune rejection of stem cell transplantation. Gene editing can exert anti-immune rejection effects by knocking out or adding genes that are associated with immunity. For example, CRISPR/Cas9 can target genes encoding immunogenic proteins, such as α -Gal, that are expressed on the surface of porcine cells[16,30]. Leung *et al*[31] transplanted hESC-derived endothelial cells with transgenic expression of murine CD47 on their cell surfaces in mice. The results showed that ectopic expression of recipient CD47 mitigates macrophage-mediated phagocytosis and improves their survival after transplantation[31]. Similarly, Diamond *et al*[32] transplanted the hearts of transgenic pigs that express high levels of human CD46 in porcine vascular endothelial cells into baboons. The results showed no hyperacute rejections[32]. However, antibodies against other non-Gal antigens were found at varying levels in the pretransplanted sera of most primates, implying that additional research needs to be conducted on this topic in the future[33].

The use of encapsulated-cell technology helps stem cells to avoid xenogeneic host immune attacks. Cell encapsulation refers to the enveloping of single or groups of cells in a polymeric biomaterial that forms membranes with semipermeable properties[1,34,35]. Miceli *et al*[34] encapsulated human amnion-derived MSCs in a semipermeable and biocompatible fiber so that the paracrine activity of these cells could promote tissue regeneration while it avoided allogeneic-related problems[34]. Orive *et al*[35] demonstrated that stem cells could generate functional pancreatic organoids to treat type 1 diabetes mellitus, while gradual loss of function and cell death were commonly detected when pancreatic organoids were transplanted in immunocompetent animals. Macro- and/or micro-encapsulations are able to improve long-term survival of pancreatic organoids generated from human cells[1,35]. The referred research studies indicate that cell-encapsulated technology is an effective method to solve the immune rejection problem.

Immunosuppressive drugs can also be used to suppress immune rejection in xenogeneic stem cell transplantation. A classic immunosuppressor is cyclosporine A, which has had reliable therapeutic effects on immune rejection in clinical practice for many years[36,37]. Compared with organ transplantation where the drugs are given systemically, the drug delivery methods in stem cell transplants are more flexible and convenient. Co-grafting a drug sustained-release system with stem cells is the most favored method. Yu *et al*[37] co-grafted cyclosporine A poly-(L-lactide) nanoparticles with human iPSCs in hemi-Parkinsonian rats. The results showed that this method exerted the desired immunosuppressive effect without any side effects[37].

Considering the role of cytokines in the immune rejection, some researchers used cytokines as candidates for the immunomodulatory tools in a xenogeneic stem cell transplantation model. Interferon- γ (IFN- γ) treatment of MSC/extracellular matrix complex upregulated indoleamine 2,3-dioxygenase expression, and thus suppressed T-cell properties *in vitro*. Xenotransplantation of IFN- γ -pretreated MSC/extracellular matrix complex without the use of an artificial scaffold retained an elevated immunomodulator capacity and induced bone regeneration in a mouse calvarial defect[38]. In addition, other cytokines such as transforming growth factor- β could be used to regulate T-cell responses[39-41].

In addition, cellular desensitization may be used as a method to suppress immune rejection. Cell desensitization refers to the desensitization achieved by repeat injections of xenogeneic stem cells into a neonatal host, so that the stem cells can survive long-term transplantation in the xenograft environment of adult host. Although the desensitization mechanism and success rate need to be discussed, Heuer *et al*'s research has demonstrated that hESC desensitization could surpass the survival time of conventional pharmacological immune-suppressive treatments[42]. Although the cell desensitization has been demonstrated in animal models only thus far, cellular or cell derivatives' desensitization offers the possibility of xenogeneic stem cell transplantation.

Cell death, abnormal differentiation, and proliferation

Similar to the problems associated with cell replacement therapy, cell death and abnormal cell differentiation and proliferation have directly led to the failure of

xenogeneic stem cell transplantation, and even harmed the recipients. Researchers have shown that the cell culture microenvironment affects cell death and differentiation. Therefore, some researchers have tried to change the microenvironment of the cells to avoid cell death and abnormal differentiation. Herein, we will discuss two common methods to alter the microenvironment of cell cultures to emulate the native growth niche *in vivo*. One method is to change the traditional two-dimensional (2D) culture to a three-dimensional (3D) culture. Qiao *et al*[43] used cell chips, a device to restrict cells to specific spatial locations, to develop single-cell derived spheres of umbilical cord MSCs. They combined a 3D culture with 2D arrayed patterns of single or multiple cells on one patch in the cell chip to (1) improve MSC survival and migration ability; and (2) promote angiogenesis in xenotransplantation[43]. The other approach involves the modification of the scaffold. For tissue-engineering-related xenogeneic stem cell transplantation, scaffold materials may play a role in cell survival and differentiation. Raynald *et al*[44] used a hyaluronic-acid-based scaffold which was covalently modified by poly-L-Lysine, as a vehicle to deliver the hBMSCs to the injured spinal cord of rats. Rats receiving hBMSCs/hyaluronic acid-poly-L-Lysine showed improved survival of transplanted hBMSCs *in vivo*[44]. McCarty *et al*[45] showed that the gel foam scaffold was supportive of chondrogenesis, while a ceramic hyaluronic acid/tricalcium phosphate carrier resulted in ectopic osteogenesis, adipogenesis, and hematopoietic-support activity in the case of sheep MSCs injected in immunocompromised rats. These findings highlighted the importance of selection of a suitable scaffold for tissue engineering considering the expected cell differentiation direction[45]. iPSCs and ESCs have potential tumorigenic properties owing to their cellular overgrowth in cell transplantation and other therapies. To solve this problem, Zygiogianni *et al*[46] implemented optimized directed differentiation protocols to yield the desired precursor cell types and utilized cellular enrichment procedures to remove unwanted cells to select only the cells with a restricted proliferation potential for transplantation[46].

Animal viruses

Although the public is concerned with animal virus transmission in xenogeneic stem cell transplantation, animal viruses are much easier to be controlled than human-to-human viral transmissions. Previous studies have demonstrated that animal viruses can be controlled with the use of effective measures, including the breeding of source animals in biosecure isolation conditions, regular testing of donor animals, and the execution of long-term follow-ups after clinical xenotransplantations[2,27,47].

For endogenous retrovirus that cannot be solved by the above methods, gene editing can be used as an effective strategy. The current research studies focus more on porcine endogenous retroviruses. CRISPR/Cas9, a revolutionary gene editing technology that allows the custom modification of almost any part of any genome with unmatched precision and accuracy, has stimulated interest in the field as it offers the possibility to genetically engineer porcine organs and tissues that are virtually risk-free of endogenous porcine retrovirus transmissions[16,30].

Ethical issues

The attitude of the public toward the ethics of xenogeneic stem cell transplantation is changing. Some people hold the view that xenotransplantation inevitably compromises species boundaries and erodes human dignity. Animal welfare groups also opposed xenotransplantation on the grounds that nonhuman animals should not be treated as redesignable systems[30]. In fact, various animal products are already used in humans. For example, bioactive bones from decellularized bovine femoral bone and freeze-dried bone marrow stem cell paracrine factors are extensively used in large-sized bone defects[48]. These achievements are gradually changing the public's outlook, paving the way for xenogeneic stem cell transplantation. However, potential applications must consider customs, laws, religions, and other factors in different regions.

CLINICAL PROSPECTS

The transplanted xenogeneic stem cells could replace directly the dysfunctional cells through *in situ* tissue-specific lineage transdifferentiation (*e.g.*, totipotent stem cells and tendon- or bone-derived lineage cells), as well as improve the endogenous regenerative milieu through the release of pro-angiogenic, proneurogenic, and anti-inflammatory factors. Therefore, xenogeneic stem cell transplantation could be used to

treat a variety of diseases (Figure 1 and Table 1).

Organ reconstruction

Xenogeneic stem cell transplantation introduces new ideas for organ reconstruction. Thus far, multiple research studies have reported its therapeutic effects in liver failure, myocardial infarction, advanced type 1 diabetes mellitus, myelosuppression, and other end-stage diseases[11-15]. Zhu *et al*[12] transplanted porcine ADSCs in acute-on-chronic liver failure rabbits. The results showed that xenogeneic stem cell transplantation significantly improved liver function and prolonged the liver survival time owing to various mechanisms such as cytokine production and inflammatory reaction inhibition. Hepatic regeneration may be associated with multiple pathways to accomplish cell replacement and organ repair[12]. Nakamura *et al*[13] injected porcine MSCs directly into the peri-infarct zones of hearts of immunodeficient mice at the time of acute myocardial infarction. The promoted functional improvement in the infarcted heart is most likely attributed to the paracrine effects of MSCs rather than because of directly induced cardiomyocyte regeneration[13]. Radtke *et al*[11] injected nonhuman primate hematopoietic stem and progenitor cells intravenously in a mouse model and demonstrated a dose-dependent multilineage engraftment of nonhuman primate hematopoietic stem and progenitor cells in the peripheral blood, bone marrow, spleen, and thymus; this enabled homing of the nonhuman primate hematopoietic stem and progenitor cells in the bone marrow stem cell niche and supported complete reconstitution of phenotypically and functionally distinct nonhuman primate hematopoietic stem and progenitor cell subpopulations[11]. Horn *et al*[14] reported low-level engraftment of gene-modified and transplanted baboon hematopoietic stem and progenitor cells with the nonobese diabetic/severe combined immune-deficient mouse model, and demonstrated that baboon hematopoietic stem and progenitor cells provide stable multilineage repopulation and differentiation of all blood cell types after transplantation as human candidate stem cells[14]. Abed *et al*[15] reported that *Macaca cynomolgus* iPSC-derived hematopoietic cells can yield hematopoietic engraftment in a cytokine stimulation protocol in immunodeficient mice[15].

In addition to the narrow sense of xenotransplantation of stem cells from animals to humans or animals that belong to another species, the so-called reverse xenotransplantation can also be used for organ reconstruction. Reverse xenogeneic stem cell transplantation takes advantage of the host animals to generate and expand human cells, tissues, and organs for transplantation. For example, to generate hepatocytes, islets, or hematopoietic cells, the human stem cells would be allowed to fully differentiate in the animal host whereupon the mature cells or tissues could be harvested and transferred to the patient with slight or no immune rejection. The generation of human iPSCs enables the access to patient-derived pluripotent stem cells and tissues/organs can potentially be generated to match the same genetic background of the patient recipient[3,23,49]. Reverse xenogeneic stem cell transplantation mainly involves gene knockouts to generate animal models that lack specific organs and blastocyst complementation to form a chimeric animal consisting of the animal and human embryo, thus potentially allowing the fabrication of human organs in animals[16,49,50]. The CRISPR/Cas9 system is the most convenient tool for gene knockouts. The blastocyst complementation method was developed to inject cells in a blastocyst. Current research studies mainly deliver human stem cells to animals through intra-uterine stem cell transplantation that averts rejection and provides a more nurturing microenvironment[3,23]. Earlier research studies of organ regeneration by blastocyte complementation mainly focused on rat blastocysts with xenogeneic (interspecific: Mouse ESC and iPSC) stem cells. Thus far, organs that have been successfully used in rat hosts have included the pancreas, heart, lung, and kidney[23,50]. Considering the development rate, anatomy, physiology, organ size, genomic similarity, and cell cycle characteristics between donor and recipient, large animals (humanized pigs) constitute good candidates as transplantation hosts to generate sizable masses of human cells, tissues, and organs for clinical purposes[16,49]. Matsunari *et al*[51] created apaucancreatic pig embryos as recipients for the complementation with wild-type donor cells, and demonstrated the feasibility of organ generation with blastocyst complementation in pigs[51]. Although research-related gene knockout studies associated with all the lung tissue types have been published, a better understanding of the nuances of pulmonary development is required before this method can be applied to pulmonary tissues[52]. In addition, before the use of chimeric human-pig embryos becomes successful, the selection of suitable human iPSCs and ethical issues should be considered. These reports demonstrated that xenogeneic stem cell transplantation has broad prospects in liver failure, myocardial infarction, advanced type 1 diabetes mellitus, myelosuppression,

Table 1 Therapeutic potential of xenogeneic stem cells in various experimental disease models

Source	Clinical condition/experimental animal model used	Observations	Ref.
Porcine ADSC	Acute-on-chronic liver failure/rabbit	Improved the liver function and prolonged their survival time	[12]
Porcine MSCs	Acute myocardial infarction/immunodeficient mouse	Promoted functional improvement in the infarcted heart most likely resulting from the paracrine effects	[13]
Baboon hematopoietic stem/progenitor cells	Nonobese diabetic/severe combined immune-deficient mouse	Provide stable multilineage repopulation and differentiation into all blood cell types	[14]
NHP hematopoietic stem/progenitor cells	Mouse	Reconstituted the bone marrow stem cell niche	[11]
<i>Macaca cynomolgus</i> iPSC-derived hematopoietic cells	Immunodeficient mouse	Yielded hematopoietic engraftment in a cytokine-stimulation protocol	[15]
Rabbit umbilical cord mesenchymal stem cells	Bilateral cranial defects/immunocompetent rat	Promoted osteogenesis by secreting BMP2 and inhibiting the inflammatory reaction	[9]
Sheep BMSCs	Ectopic implantation/immunocompromised mouse	Extensive bone formation	[58]
Ovine MSCs	Ectopic implantation/immunocompromised mouse	Ectopic osteogenesis, adipogenesis and haematopoietic-support activity (with a ceramic HA/TCP carrier); partial chondrogenesis (within a gelatin sponge)	[45]
Porcine NPCs	Intravenous pentylenetetrazole seizure threshold test/rat	Widespread migration and inhibitory interneurons	[55]
Porcine ESCs	Spinal cord injury rat	Functional recovery of hindlimbs and exhibition of the highest BBB scale score	[27]
Pig embryonic neural precursor cells	Parkinson's disease/ <i>Macaca fascicularis</i>	Long-term xenograft survival and differentiation; significant improvement of locomotor activity	[54]
Porcine neural stem/precursor cells	Parkinson's disease/rat	Exhibited large and healthy grafts; improvement in recovery neurological function and survival	[29]
Miniature-swine neural stem cells	Parkinson's disease/rat	Functional recovery from Parkinson's disease behavioral defects; the graft revealed multiple types of neurons	[18]
Porcine UCMSC	Parkinson's disease/rat	Engrafted and proliferated without immune rejection; differentiated into TH-positive cells	[28]

ADSC: Adipose-derived stem cell; MSCs: Mesenchymal stem cells; NHP: Nordic hamstring protocol; iPSC: Induced pluripotent stem cells; BMP2: Bone morphogenetic protein 2; BMSCs: Bone marrow mesenchymal stem cells; HA/TCP: Hydroxyapatite/beta-tricalcium-phosphate; NPCs: Nucleus pulposus cells; ESCs: Embryonic stem cells; BBB: Blood-brain barrier; UCMSC: Umbilical cord mesenchymal stem cell.

and other end-stage diseases.

Neurological diseases

Xenogeneic stem cell transplantation provides a novel pathway for diseases that cannot be solved by organ transplantation, such as neurological diseases represented by Parkinson's disease[53]. Badin *et al*[54] transplanted pig embryonic neural precursor cells in the striatum of immunosuppressed Parkinsonian primates that resulted in long-term xenograft survival and differentiation, in conjunction with significant improvements in locomotor activity[54]. Michel-Monigadon *et al*[29] transplanted porcine neural stem/precursor cells into the striatum of rats without immunosuppression. The cells yielded large and healthy grafts and led to significant improvements/recovery of neurological function and survival[29]. Backofen-Wehrhahn *et al*[55] demonstrated that bilateral transplantation of neural precursor cells derived from porcine and human ventral mesencephalon in the subthalamic nucleus of immunosuppressed rats induces anticonvulsant effects. All these cells showed widespread migration characteristics, developed characteristics of inhibitory interneurons, and survived for up to 4 mo after transplantation[55]. Mine *et al*[18] transplanted miniature-swine mesencephalic neuroepithelial stem cells from the midbrain at early embryonic stage in the Parkinsonian rat striatum. The cells can survive, differentiate into functional neurons, form synaptic connections with the host brain, and ameliorate neurological dysfunction only during the 1-wk administration of

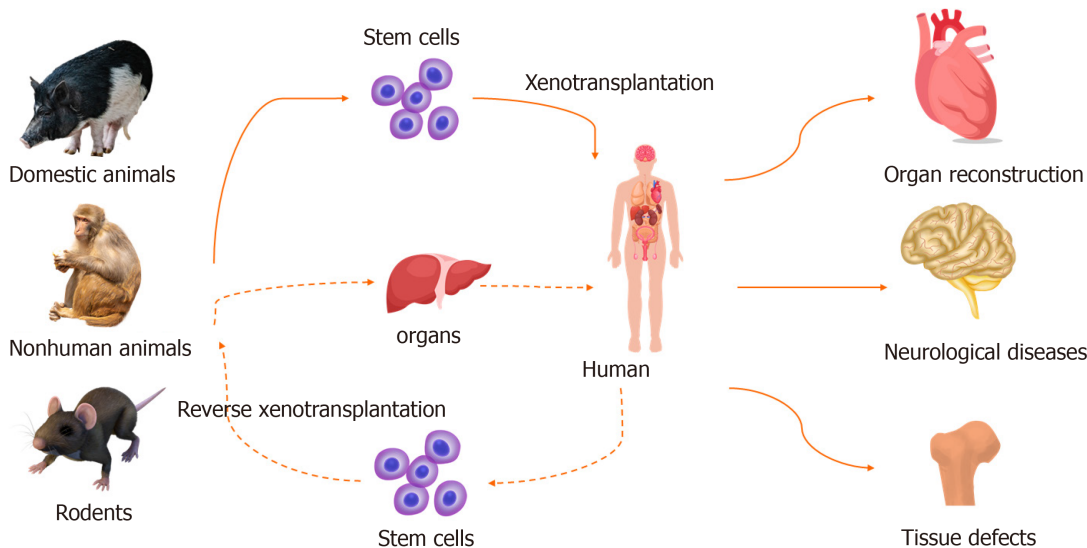


Figure 1 Xenogeneic stem cell transplantation and reverse xenotransplantation.

immunosuppressants[18]. Yang *et al*[27] transplanted porcine embryonic stem-derived neuronal progenitors in spinal cord injury model rats and demonstrated the treatment potential of grafted cells for spinal cord injury and functional behavioral improvement[27]. Similarly, Medicetty *et al*[28] transplanted porcine umbilical cord MSCs in the lesioned brains of rats affects by Parkinson's disease, and the cells proliferated normally and differentiated into tyrosine hydroxylase-positive cells[28]. Fink *et al*[56] and Schumacher *et al*[57] have transplanted porcine fetal neural cells unilaterally in Parkinson's and Huntington's disease patients, and observed clinical improvement and favorable safety profiles[56,57]. These research studies showed that xenogeneic stem cells could serve as an attractive candidate for neural transplantation.

Tissue defects

Xenogeneic stem cell transplantation has broad prospects in tissue defects. Tissue defects can be caused by trauma, tumor, and birth defects, which severely impair daily and social lives of patients[9,17,19]. Many researchers have demonstrated that xenogeneic stem cell transplantation with scaffolds could treat bone, cartilage, and soft tissue defects. Kon *et al*[58] and McCarty *et al*[45] independently transplanted sheep BMSCs ectopically with different carriers in immunocompromised mice. Both studies showed that xenogeneic stem cells induced chondrogenesis, osteogenesis, adipogenesis, and hematopoietic-support activity[45,58]. Li *et al*[9] transplanted rabbit umbilical cord MSCs into rats and showed that xenogeneic stem cells promote osteogenesis by secreting bone morphogenetic protein 2 and inhibiting the inflammatory reaction in xenogeneic rat hosts of bilateral cranial defects[9]. In addition, porcine synovial MSCs were cultured to develop 3D cell/matrix constructs, which were transplanted in an allogenic meniscus defect model that resulted in fibrous- or chondrogenic-tissue-like repairs[21,22]. Autogenous porcine BMSCs/ engineered collagen tissue can also be used to treat osteochondral defects *in vivo*[59].

CONCLUSION

Xenogeneic stem cell transplantation has the advantages of (1) Potentially unlimited supply; (2) Convenient acquisition; (3) Achievable quality control; and (4) Lower cost, thus establishing the basis for large-scale clinical applications. Prior research studies have demonstrated that xenogeneic stem cell transplantation has significant therapeutic effects and broad application prospects in treating liver failure, myocardial infarction, advanced type 1 diabetes mellitus, myelosuppression, and other end-stage diseases based on the direct replacement of the dysfunctional cells or the improvement of the endogenous regenerative milieu. Although there remain potential problems in xenogeneic stem cell transplantation, researchers have conducted numerous studies to solve these issues. Therefore, xenogeneic stem cell transplantation provides a new

strategy for end-stage diseases and is worthy of intensive investigations in the future.

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