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Current Status in Peripheral Nerve Xenotransplantation

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Abstract

Nerve grafts are used to repair segmental defects in peripheral nerves. However, autografts and even allografts are limited for clinical use. Xenotransplantation offers a potentially unlimited source for tissue transplantation. We have conducted a systematic review of the literature, aiming to clarify the latest and more appealing proposals and discoveries in nerve xenotransplantation. A total of 22 articles were retrieved, all of them experimentally controlled studies in animals. There are no current studies in humans. Fresh xenografts provoke an immune response that leads to graft rejection. Immunosuppressive drugs or pretreatment of the grafts are the preferred methods against immune rejection. Recently, investigative groups have proposed the use of acellular nerve xenografts, which do not elicit immune rejection while they do allow and promote axonal regeneration. The addition of human stem cells increases nerve growth. Limits to the analyzed studies are the absence of trials in humans and the short length of the nerve defects that have been successfully repaired. Further investigations and clinical trials are needed before nerve xenografting is accepted as a valid method of nerve repair.

Keywords: heterologous transplantation, immune tolerance, nerve repair, peripheral nerves, stem cells, xenografts

1. Introduction

Nerve grafts are used to bridge defects in peripheral nerves that cannot be repaired by direct suturing. However, autografts and even allografts are limited for clinical use. The ready availability of xenografts has put them in the center of clinical surgery research as an alternative graft strategy.

Xenotransplantation offers a potentially unlimited source for tissue transplantation, but with the obvious drawback of immune rejection. Many groups are investigating the molecular, immunologic, biologic, and cellular aspects of xenotransplantation and have proposed various

techniques and approaches to perfect the composition of the transplanted tissue and to modulate the immune response, in an attempt to find the perfect nerve xenograft.

We have conducted a systematic review of the literature, aiming to clarify the latest and more appealing proposals and discoveries in nerve xenotransplantation, which we detail in the following text.

2. Systematic review

We searched PubMed and Embase databases, using the combined search terms “xenotransplantation” or “heterologous transplantation” and “peripheral nerve.” We screened titles and abstracts and decided which articles to retrieve. Articles were also identified by a manual search of bibliographies from all retrieved articles. Studies were eligible for inclusion if they addressed both heterologous transplantation and peripheral nervous system. Only articles with English language abstracts were included. For those articles that were not available in English, only the content of the abstracts was analyzed. Excluded studies were those addressing the central nervous system. No limits were placed on publication date or study design.

3. Results

A total of 22 articles were retrieved, all of them experimentally controlled studies in animals. Most studies used rats as host species [1–15]. Four studies used mice [16–19]. The most commonly used nerve for the nerve defect was the sciatic nerve [2, 3, 5, 8–10, 12–19]. As for donor species, New Zealand rabbits [1, 3, 6, 12] and Sprague-Dawley rats [16–19] were the most commonly used. One study compared the outcomes using different species [9]. One study used human nerves (sural nerve) [9]. Six studies used human mesenchymal stem cells laden in autologous or synthetic conduits [8, 10, 13–15, 20]. There have been no studies with humans as recipients for xenografts.

Table 1 shows the details of the species and nerve defects used in each study.

Sample size ranged from 6 to 96. Follow-up time ranged from 2 to 360 days. **Table 2** shows details of the sample size, follow-up time, and type of graft used.

3.1. Type of graft

Of the 22 retrieved articles, 7 described a study in which nerve defects were repaired with fresh nerve xenografts [4, 7, 16–19]. Six studies used acellular nerve xenografts [1–3, 6, 9]. Two used both fresh xenografts and acellular xenografts [11, 12]. Six studies used biological or synthetic conduits seeded with xenogeneic cells [8, 10, 13–15, 20]. One of the articles does not specify the type of graft used [21].

Among the studies that used acellular nerve xenografts, different extraction procedures were used. Two studies compare results with the extraction procedure as a variable [9,12].

	Reference	Host	Donor	Gap (mm)
1	Hebebrand et al. [5]	Lewis rat (sciatic n)	Golden Syrian hamster (sciatic n)	5
2	Hebebrand et al. [21]	?	?	?
3	De Vaconcellos et al. [11]	Sprague-Dawley rat (median n)	Beagles dog (antebrachial cutaneous n)	10
4	Li et al. [12]	Sprague-Dawley rat (sciatic n)	Rabbit (tibial n)	15
5	Udina et al. [19]	OF1 mouse (sciatic n)	Sprague-Dawley rat (peroneal n)	6
6	Choi and Raisman [4]	AS strain rat (facial n)	Balb-C mouse (sciatic n)	7–8 versus 15–20
7	Lu et al. [7]	Sprague-Dawley rat (peroneal n)	Balb-C mouse (sciatic n)	10
8	Zhang et al. [2]	Sprague-Dawley rat (sciatic n)	York pig (intercostal n)	10
9	Kvist et al. [9]	Wistar rat (sciatic n)	Frog <i>Rana temporaria</i> , NRMI mouse (sciatic n), human (sural n), pig <i>Suidae Yorkshire</i> (tibial n)	7
10	Jia et al. [3]	Wistar rat (sciatic n)	New Zealand rabbit (?)	10
11	Yu et al. [16]	Balb-C mouse (sciatic n)	Sprague-Dawley rat (sciatic n)	5
12	Huang et al. [22]	Rhesus monkey (radial n)	Landrace pig (tibial n)	25
13	Zhu and Lou [1]	Wistar rat (facial n)	New Zealand rabbit (facial n)	6
14	Sakar et al. [14]	Sprague-Dawley rat (sciatic n)	Human cells	10
15	Gärtner et al. [13]	Sprague-Dawley rat (sciatic n)	Human cells	–
16	Chai et al. [18]	C57 BL6 mouse (sciatic n)	Sprague-Dawley rat (sciatic n)	20
17	Tremp et al. [8]	Sprague-Dawley rat (sciatic n)	Human cells	10
18	Huang et al. [6]	Wistar rat (facial n)	New Zealand white rabbit (facial n)	10
19	Lasso et al. [20]	New Zealand rabbit (peroneal n)	Human cells	40
20	Zarbaksh et al. [10]	Wistar rat (sciatic n)	Human cells	10
21	Yu et al. [17]	Balb-C mouse (sciatic n)	Sprague-Dawley rat (sciatic n)	5
22	Masgutov et al. [15]	Rat (sciatic n)	Human cells	10

Table 1. Detail of the species and nerve defects used in each study.

In general, the consensus is that fresh xenografts provoke an immune response [5, 16–18] that leads to graft rejection [7, 11, 12, 19]. Choi and Raisman [4] conclude that in short nerve gaps of 7–8 mm, regeneration can occur in spite of the immune rejection, without the need for immunosuppressant drugs, but longer defects of 15–20 mm require immunosuppression to

	Reference	Sample	Follow up (days)	Type xenograft
1	Hebebrand et al. [5]	?	?	Fresh xenograft ± FK506/RS61443
2	Hebebrand et al. [21]	?	?	?
3	De Vaconcellos et al. [11]	60	360	ANX versus fresh xenograft
4	Li et al. [12]	30	180	ANX versus fresh xenograft
5	Udina et al. [19]	35	21	Fresh xenograft ± FK506
6	Choi and Raisman [4]	96	84	Fresh xenograft ± cyclosporine
7	Lu et al. [7]	30(?)	56	Fresh xenograft
8	Zhang et al. [2]	6	90	AXN + autoADSC
9	Kvist et al. [9]	53	10	ANX
10	Jia et al. [3]	50	56	ANX + BMSC
11	Yu et al. [16]	48 (?)	30	Fresh xenograft
12	Huang et al. [22]	10	150	ANX + autoADSC
13	Zhu and Lou [1]	40	140	ANX
14	Sakar et al. [14]	27	56	hMSC
15	Gärtner et al. [13]		140	hUCSC
16	Chai et al. [18]	200(?)	28	Fresh xenograft
17	Tremp et al. [8]	13	28	Fibrin conduit + hADSC or hSVF
18	Huang et al. [6]	18	84	ANX
19	Lasso et al. [20]	60	90	Vein graft ± Cyclosporine ± hADSC
20	Zarbakshsh et al. [10]	24	84	Silicone conduit ± autoBMSC ± hUCSC
21	Yu et al. [17]	?	3	Fresh xenograft + BDNF
22	Masgutov et al. [15]	29	65	hADSC

ANX, acellular nerve xenograft; hADSC, human adipose-derived stem cells; ADSC, adipose-derived stem cells; BMSC, bone marrow stem cells; BDNF, brain-derived neurotrophic factor; hSVF, human stromal vascular fraction; hUCSC, human umbilical cord stem cells; hMSC, human mesenchymal stem cells.

Table 2. Detail of sample size, follow-up time, and type of graft used.

achieve nerve growth. Acellular nerve xenografts do not elicit an immune response [22] and can therefore be used to bridge nerve defects without immunosuppressant drugs with good results [1–3, 6, 9, 11, 12, 22].

Nerve conduits are useful for nerve restoration. Xenogeneic stem cell-laden conduits prove an increased regenerative ability [8, 10, 13–15, 20].

3.2. Immunosuppression

There is a total of four studies that compare the outcomes with or without the use of immunosuppressive drugs (two use Cyclosporine A, two use FK506) [4, 5, 19, 20]. Immunosuppressant

treatment with cyclosporine A, FK506, or RS61443 can reduce acute graft rejection and allow nerve regeneration [4, 5, 19].

Two studies propose that specific antibodies against interleukins could also be useful in decreasing graft rejection [16, 18].

Among the studies that use xenogeneic cells only, one compares outcomes with and without immunosuppressive therapy [20]. Tremp et al. [8] and Zarbakhsh et al. [10] suggest that human stem cells act as immunosuppressants, with an ability to induce the production of anti-inflammatory cytokines, and they therefore do not use immunosuppressive drugs.

3.3. Defect length

The nerve defect ranged from 5 to 25 mm in the studies that used xenografts and up to 40 mm in one study that used vein grafts laden with human adipose-derived stem cells (hADSC) [2].

The length of the gap that has been successfully bridged is 7–8 mm with unprocessed xenografts [4], 25 mm with acellular nerve grafts [5], and 40 mm with vein conduits seeded with hADSC [20]. The consensus is that only short gaps can reach complete regeneration with a xenograft, and further studies are required to find a viable conduit that bridges longer nerve gaps with a tolerable immune response.

4. Discussion

Nerve grafting was first reported by Philipeaux and Vulpian in 1870. The first human nerve graft was reported by Albert in 1878. For decades, research has advanced in favor of autografts, with progress being made in the understanding of nerve biology and chemical mechanisms involved in nerve repair and the perfecting of suture and surgical techniques. But although autologous nerve grafting is ideal, it has some obvious disadvantages, such as lack of availability and donor-site morbidity. For this reason, investigations turned to nerve allografts. Attempts to reduce the rejection of nerve allografts have focused on either nerve graft pretreatment or host immunosuppression [23–25]. The results have not reached those of autografting, and even allografts are a limited source. The ready availability of xenografts has recently put them in the center of clinical surgery research as an alternative graft strategy.

Much of the current research is focused on the study of host immune response to xenografts, as well as the genetics and biochemical reactions involved in graft integration. The immune response to nerve xenotransplantation is poorly understood; most of the research is based on the existing knowledge of nerve allografts.

Peripheral nerves are composed of nerve axons, fibroblasts, Schwann cells, and extracellular matrix. Host Schwann cells are critical for nerve regeneration and production of neurotrophic factors and, Schwann cells of long nerve grafts are also involved in the regenerative process [26]. But donor Schwann cells are one of the most immunogenic components of nerve allografts [27, 28] and it is immune rejection and the scar tissue that is formed due to the immune response that inhibits axon regeneration [29]. To reduce this reaction, allografts have been pretreated to

decrease their antigenicity, but these treatments also reduce Schwann cell viability [30]. Recent studies are moving away from nerve graft pretreatment and toward investigating other mechanisms of immune response suppression.

Lu et al. [7] described the importance of cellular immune responses in xenograft rejection. They also described the limitations in xenografting of cold preservation of the grafts as a way to decrease rejection, a method frequently used in allografting.

Of the same group, Yu et al. [16] proved that xenograft rejection is mediated especially by interferon-gamma (IF γ)-producing Th1 cells and IL17-producing Th17 cells. They suggested that the rejection of a xenograft can be prevented after treatment with IL17 and IF γ -neutralizing antibodies. In a recent study [17], they proposed brain-derived neurotrophic factor as a promising inhibitor of peripheral nerve xenograft rejection. Chai et al. [18] studied the significance of Th22 and Treg cells interaction in the regulation of xenograft rejection.

Based on these studies of immune response, trials have been made using different types of immunosuppressive drugs. Choi and Raisman [4] propose that there is a limit distance that nerve regeneration through a xenograft is able to cover against acute host rejection, but to grow further it requires the assistance of immunosuppression (their experiments are carried out on facial nerve grafts from mouse to rat).

Hebebrand [5, 21] proved increased nerve regeneration through xenografts with immunosuppression with FK506 and RS61443 based on the knowledge that they have on neuroregenerative and neuroprotective effects independent of their immunosuppressive activity. Udina et al. [19] proved that a 5-mg/kg/day dose of FK506 is necessary to achieve nerve regeneration in rat to mice xenografts, as opposed to a 2-mg/kg/day dose for allografts.

There are no clinical studies in humans. Magnusson et al. [31] proposed to begin the study of pig to human xenotransplantation by describing the xenoantigenic pattern on porcine peripheral nerve.

A different line of research regarding peripheral nerve repair has focused on the application of biologic or synthetic nerve conduits [32]. Donor-site morbidity is reduced, as is surgery time, and the problem of rejection is avoided. The ideal properties of a nerve conduit are biocompatibility, biodegradability, neuroinductivity, and neuroconductivity. The last two properties can be enhanced by adding host or xenogeneic multipotent stem cells with the ability to produce the necessary growth factors. Bone marrow stromal cells (BMSCs), human umbilical cord stromal cells (HUCSCs), undifferentiated, and adipose-derived stem cells have been studied, with different results [8, 10, 13–15, 20, 33]. Zarbakhsh et al. [10] conducted a study with 24 Wistar rats, where 10-mm gaps in the sciatic nerve were bridged with a silicone conduit with added bone marrow stromal cells, human umbilical cord stromal cells or no cells. He concluded that both auto-BMSCs and xeno-UCSC have the potential to regenerate peripheral nerve injury and that BMSCs are more effective than HUCSCs in rat. As opposed to other xenogeneic cells, stem cells did not seem to provoke an immune response in the host after transplantation [34, 35].

Silicone or fibrin scaffolds, or even veins, only provide a physical conduit for nerve regeneration. But the goal is to provide a conduit that is also able to produce the adequate molecular signals that promote cell differentiation, migration, and axonal elongation. This can only be achieved using peripheral nerves as nerve grafts. Therefore, the aim of investigators has been to find or create a non-immunogenic xenograft. Acellular xenografts are created chemically eliminating the cellular constituents that cause immunogenic reactions but preserving the native extracellular matrix, which retains sufficient bioactivity to promote axon regeneration [36].

Huang et al. [22] used acellular xenografts with allogenic adipose-derived stem cells in rhesus monkey, obtaining no immune response to the grafts. They later conducted a study in rat facial nerve defects, achieving similar results to those obtained with allografts [6]. Similar results were reported by Zhu et al. [1].

In 2010, Zhang et al. [2] reported that acellular nerve xenografts, similar to acellular nerve allografts (ANAs), are immunocompatible. He also proposed that short defects can regenerate along acellular scaffolds but that longer defects might require certain cellular impulses, which should be provided by added autologous stem cells.

Li et al. [12] repaired rat sciatic nerve gaps with acellular xenogeneic scaffolds, with good results.

Jia et al. [3] transplanted acellular nerve allografts and rabbit xenografts (ANX), with and without BMSC enhancement, into rat sciatic nerve gaps, comparing the different groups with autografts. They concluded that ANX implanted with BMSCs had a functional rehabilitation efficacy comparable to autografting.

De Vaconcellos et al. [11] repaired 2 cm median nerve gaps in rats with Beagle dog acellular frozen xenografts, managing a correct but slow regeneration, and thus suggesting that freezing suppresses the immune reaction but produces a deficient environment.

Kvist et al. [9] studied the differences in acellular xenografts from different species (frog, mice, human, and pig) transplanted into rat sciatic nerve gaps, proposing differences in axonal outgrowth which should be further studied before clinical use.

All existing studies have a clear limitation regarding the species in which the experiments are carried out on. No studies used humans as hosts, and only one study included human sural nerves as donor for xenografting. Unlike organ transplantation, peripheral nerve grafting does not usually occur in a scenario of urgency, and nerve injury is not life-threatening. Thus, nerve xenografts can only be considered in real clinical situations when benefits are heavier than the risks associated to immunosuppression and even cross-species disease transmission.

The future moves toward a xenograft that is immunocompatible—probably acellular, seeded with xenogeneic stem cells or similar growth factor-producing elements—with no need of immunosuppressive therapy. Also, advance has to be made in the way of creating longer grafts or ways to make the process of regeneration occur fast enough to achieve a complete axonal growth in longer defects before scarring and inflammation block nerve advancement.

5. Conclusions

Most of the existing studies on nerve xenografting concur in their results of peripheral nerve xenotransplantation, which are found to be similar to those reached with nerve allografts and acceptable, though lower, compared to the results of autografting. The scenario in which these results can be reached are in all cases similar, defects of 5–25 mm in peripheral nerves, of rats or rabbits mostly, repaired with either fresh xenografts—supplemented with immunosuppressive therapy—or acellular grafts. The direction in which all investigations move is toward adding stem cells or other sources of growth factors that might improve the reach of axonal growth. A long way still separates us from creating a graft that will work in humans.

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