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Editorial

Segmental Defects in Peripheral Nerves Xenotransplantation

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Editorial

Segmental defects in peripheral nerves that cannot be sutured directly require the use of nerve grafts. The ideal option for repair is nerve auto grafting, but there are some obvious disadvantages related to its use, such as lack of availability and donor site morbidity. The next step to consider for reconstruction is the use of nerve allografts, but they are also limited for clinical use, and they present with the added problem of graft rejection. Considering these limitations to the use of nerve autografts and allografts, clinical surgery research has turned to nerve xenotransplantation, which offers a potentially unlimited source of donor nerves.

We conducted a review of the literature, aiming to clarify the present situation regarding peripheral nerve xenotransplantation and to summarize the latest proposals and investigative directions. The molecular and biochemical reactions involved in graft integration as well as the host immune response to xenografts are at the center of current research.

A nerve graft acts as a biological scaffold that allows and directs axon regeneration. However, in xenografts, immune rejection and the scar tissue that is formed due to the immune response inhibits axon growth [1]. Of the main components of a peripheral nerve, Schwann cells — both host and donor cells — are the critical elements for nerve regeneration and production of neurotropic factors, but donor Schwann cells are one of the most immunogenic components of nerve grafts. To reduce immune reaction, graft pretreatment to decrease antigenicity has been proposed; however, these treatments also reduce Schwann cell viability [2]. Different methods have been described, but due to the lack of satisfactory results recent research is leaving behind graft pretreatment and moving towards other mechanisms of immune response suppression. Many investigations have aimed to clarify the molecular components of graft rejection. Some of the elements involved have been identified, such as interferon-gamma (IFy)-producing Th1 cells and IL17-producing Th17 cells. Therefore, treatment with IL17 and IFy neutralizing antibodies could reduce nerve xenograft rejection. Other proposed inhibitors of the immune response to nerve xenografts have been brain-derived neurotrophic factor and immunosuppressive drugs FK506 and RS61443 [3]. Studies show that higher doses are needed to achieve immunosuppression with xenografts than those used with nerve allografts [4]. One study proposed that there is a limit distance of 7 mm to 8 mm that nerve regeneration through a xenograft is able to cover against acute host rejection without immunosuppression [5].

Another approach to peripheral nerve repair is the use of biologic or synthetic nerve conduits, which do not cause immune rejection and allow a reduction of donor site morbidity and surgery time. A nerve conduit must be biocompatible and it must have the capacity to produce the adequate molecular signals that promote cell differentiation, migration and axonal elongation (neuroinductivity and neuroconductivity).

To achieve neuroinductivity and neuroconductivity, many groups have proposed different approaches. Some investigators use a synthetic or biological nerve conduit with added host or xenogeneic multipotent stem cells. Bone marrow stromal cells (BMSCs), human umbilical cord stromal cells (HUCSCs), undifferentiated and adipose-derived stem cells have been studied. Zarbakhsh et al. [6] conducted a study in which 10 mm nerve gaps in rats were bridged with a silicone conduit with added bone marrow stromal cells (BMSC), human umbilical cord stromal cells (HCUCSCs) or no cells. He concluded that both auto-BMSCs and xenoUCSC have the potential to regenerate peripheral nerve injury and that BMSCs are more effective than HCUCSCs in rat. As opposed to other xenogeneic cells, stem cells did not seem to provoke an immune response in the host after transplantation. Other groups have proposed the use of acellular xenografts. Acellular xenografts are created by chemically eliminating the cellular constituents that cause immunogenic reactions but preserving the native extracellular matrix, which retains sufficient bioactivity to promote axon regeneration [7]. Zhang et al. [8] reported that acellular nerve xenografts, similarly to acellular nerve allografts, are immunocompatible. They also proposed that short defects can regenerate along acellular scaffolds but that longer defects might require certain cellular impulses that should be provided by added autologous stem cells. The results in terms of functional rehabilitation efficacy of these grafts have been proved comparable to autografting [9].

All present lines of investigation are limited to animal experimentation. There is only one study in the literature that includes human sural nerves as donor grafts and none with humans as graft receptors. With organ transplantation, the risks of immunosuppression are assumed due to urgent or life-threatening situations. But this is not the case of peripheral nerve injuries and, therefore, nerve xenografts could only be considered when the risks associated to immunosuppression and even cross-species disease transmission has been completely eliminated. Differences have also been observed depending on the donor and host species used; the reasons for these differences should be further studied and understood before human investigations can be considered [10].

Another limitation is defect length. The longest defects repaired successfully have been 40 mm [11].Future research will move towards the perfection of existing xenograft models, to create an acellular xenograft that is immunocompatible, not requirig immunosuppressive therapy, seeded with growth factor-producing elements such as xenogeneic stem cells and that can be made to fit the length of the existing defect.

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