Review

Functional and immunological peculiarities of peripheral nerve allografts

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Abstract

This review addresses the accumulating evidence that live (not decellularized) allogeneic peripheral nerves are functionally and immunologically peculiar in comparison with many other transplanted allogeneic tissues. This is relevant because live peripheral nerve allografts are very effective at promoting recovery after segmental peripheral nerve injury via axonal regeneration and axon fusion. Understanding the immunological peculiarities of peripheral nerve allografts may also be of interest to the field of transplantation in general. Three topics are addressed: The first discusses peripheral nerve injury and the potential utility of peripheral nerve allografts for bridging segmental peripheral nerve defects via axon fusion and axon regeneration. The second reviews evidence that peripheral nerve allografts elicit a more gradual and less severe host immune response allowing for prolonged survival and function of allogeneic peripheral nerve cells and structures. Lastly, potential mechanisms that may account for the immunological differences of peripheral nerve allografts are discussed.

Key Words: allograft; animal model; immunology; neuroimmunology; peripheral nerve injury; regeneration; repair; tissue regeneration; tissue transplantation; transplant

Introduction

The most common neuronal dysfunction is traumatic peripheral nerve (PN) injuries consisting of segmental defects (Bergmeister et al., 2020). Humans (and experimental laboratory animals) with segmental defects experience: (a) immediate complete loss of sensory and motor functions mediated by the denervated structures, (b) followed by rapid Wallerian degeneration of severed distal axonal segments within only a few days from injury, and (c) slow (~1 mm/day) natural regeneration by outgrowths that produce poor (if ever) functional recovery due in part to non-specific reinnervation and/or to muscle atrophy or deterioration of nerve target structures before re-innervation (Wang et al., 2019).

The ideal bridge for a segmental defect is currently an autologous nerve of similar sensorimotor composition, axonal number and axon organization as the injured nerve (Brooks et al., 2012; Kornfeld et al., 2019). As nerves with motor axons are generally not available for autografting, autografts of sensory nerves are the most effective clinical option. However, biodegradable conduits and decellularized allografts can be effective for smaller segmental defects, albeit less effective than sensory autografts (Isaacs and Browne, 2014). Decellularized allografts are processed specifically to reduce or eliminate their immunogenicity. We would point readers to other recent publications detailing the immunogenicity and clinical use of decellularized allografts (Sun et al., 2006; Lovati et al., 2018; Pan et al., 2020).

If live peripheral nerve allografts (PNAs) were not immunogenic, there are several ways they could be more effective than sensory autografts. First, PNAs recovered and stored from donor cadavers would not incur morbidity on the host. Second, PNAs can be sensorimotor matched to the defect site, producing superior regeneration of motor axons than with sensory-only grafts (Madison et al., 2007). The reasons why such matched nerves promote superior regeneration than purely sensory nerves are not completely understood, but motor-associated Schwann cells (SCs) appear to intrinsically differ from sensor-associated SCs and promote superior regeneration and pathfinding of motor axons (Löw et al., 1994; Bolivar et al., 2020).

Third, PNAs can be anatomically matched for diameter, length, fascicular organization and branching patterns, which are often important factors in successful reinnervation for regeneration. Anatomical mismatching increases the chances for inferior regeneration, fibrosis, neuromas, random target reinnervation and poorer functional outcomes (Ray and Mackinnon, 2010; Safa et al., 2020). Matching of axon number and density to the defect is also likely a key consideration for maximizing axonal fusion across segmental defects. Fourth, PNAs can be harvested to match complex nerve structures, such as branch points (Santos Roballo et al., 2019). There is no other strategy to repair segmental PN defects that include branch points.

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The Utility and Functional Peculiarity of Peripheral Nerve Allografts

Functional differences of peripheral nerve allografts

The goal for transplanting allogeneic mammalian tissues such as heart, liver, kidney, lungs or cornea is to maintain the function donor cells or structures to replace those lost in the host. PNAs used to bridge segmental PN defects are distinct in this respect because restoration of function is entirely dependent upon establishing functional host axons that extend through the PNA and connect to distal host innervation targets. The PNA is therefore a temporary scaffold for the regeneration and/or restoration of host axons and does not need to be a long-term replacement of lost host cells or structures. For segmental PN defects this can be accomplished with a PNA either by stepwise axonal regeneration or, as recently shown, through immediate axonal fusion after injury (Mikesh et al., 2018; Smith et al., 2020). Once host axon integrity through the allograft is established, host axon function appears to be maintained even as donor-origin cells are targeted and eliminated by the host immune response. This will be discussed in more detail below.

Indications of a Peculiar Immune Response to Peripheral Nerve Allografts

The host immune response to transplanted tissues

Rejection of transplanted tissue is generally initiated by a local innate inflammatory response that potentiates a subsequent adaptive response (Gunasekaran et al., 2017). Macrophages and resident dendritic cells promote inflammation and help recruit adaptive immune cells, such as T cells, to release inflammatory cytokines, chemokines and reactive oxidative species that exacerbate tissue damage (Muller et al., 2006; Gunasekaran et al., 2017). Macrophages and dendritic cells acting as antigen presenting cells (APCs) further activate T cells to specifically target the grafted tissue. This occurs either by direct allorecognition, where major histocompatibility complexes (MHCs) on donor-origin passenger APCs are recognized as foreign directly by host T cells, or indirect allorecognition where host APCs activate host T cells based upon minor histocompatibility antigen (mHA) differences (Marino et al., 2016). In both cases, populations of graft-specific T cells will expand and mediate acute graft rejection (Naik and Shawar, 2020; Ronca et al., 2020). Immediate innate rejection of allografts can sometimes rapidly occur via pre-existing alloantibodies specific for blood or polymorphic MHC antigens (hyperacute graft rejection) (Alelign et al., 2018; Ronca et al., 2020). Little can be done to stop this process once initiated and it will result in the complete destruction of the allogeneic tissue.

Innate and adaptive rejection of PNAs is typically prevented by chronic treatment with systemic immunosuppressants. The drugs cyclosporine A (CsA) and tacrolimus (FK506) have become the backbone of immunosuppression for tissue transplantation. Both drugs inhibit the serine/threonine phosphatase calcineurin, preventing calcineurin from dephosphorylating nuclear transcription factor of activated T cells (Matsuda et al., 2000). Dephosphorylation of nuclear transcription factor of activated T cells is a key step in T cell activation. These drugs have had a transformative effect on transplantation, but chronic systemic immunosuppression with these drugs is toxic for the body, and is associated with side-effects, such as opportunistic infections, increased risk of diabetes, malignancy, and renal failure (Sen et al., 2019; Roberts and Fishman, 2020).

PNAs with no or only limited immunosuppression

A common control group in PNA studies is an allograft implanted into a segmental defect without immunosuppressants. The outcomes for these control groups have been mixed, with some failing to show regeneration (Strasberg et al., 1996) while others shown in **Table 1** achieved varying degrees of permanent regeneration without immunosuppression. However, the degree of axon regeneration without immunosuppression was generally inferior to that achieved by positive control groups of an autograft and/or a PNA with immunosuppression. This outcome of significant, albeit partial, regeneration in PNAs without immunosuppression is very different than for other transplanted allogeneic tissues, which completely fail within weeks – the cornea being a notable exception due to its low cellularity and implantation in an immune privileged location, which is not the case for PNAs (Tan et al., 2012).

Other studies have shown that immunosuppression need not be continuously maintained with PNAs for full regeneration equal to autograft or PNA with immunosuppression to be achieved. **Table 2** summarizes the key aspects of these studies. The first of these was a 30-week study that showed axon regeneration across a 2 cm sciatic PNA in rats was equivalent when CsA was only provided for the first 12 of the 30 weeks compared to continuously over the entire 30 weeks (Midha et al., 1993). This phenomenon was replicated in rats by other groups and shown to be effective in monkeys and humans, even for segmental defects of 20 cm or greater. One

Table 1 | **Comparison of regeneration in non-immunosuppressed peripheral nerve allografts (PNAs) to that of control groups in various species**

Species	Graft length	Time point	Outcome measure	Comparator control group	PNA performance (% comparator)	Reference
Mouse	8 mm tibial	6 wk	# Myelinated fibers	Allograft + continuous FK506	75%	Kim et al., 2014
Mouse (Shiverer)	1 cm sciatic	14 wk	# Myelinated fibers	Allograft + continuous CsA	189%	Midha et al., 1994
Rat	1 cm sciatic	16 wk	Plantar CMAP amplitude	Matched autograft	85%	Roballo and Bushman, 2019
Rat	2 cm sciatic	20 wk	Plantar CMAP amplitude	Matched autograft	60%	Santos Roballo et al., 2019
Rat	2 cm sciatic	30 wk	Direct NAP amplitude	Allograft + continuous CsA	78%	Midha et al., 1993
Rat	3 cm sciatic	16 wk	Sciatic functional index	Matched autograft	~80%	Evans et al., 1999
Rabbit	2 cm median	7 wk	Histological indications of axons	Allograft + continuous CsA	Graded as mild *vs.* comparator	de la Monte et al., 1988
Rabbit	3 cm sciatic	5 mon	# Myelinated fibers	Matched autograft	~54%	Amillo et al., 1995
Sheep	8 cm median	10 mon	# Myelinated fibers	Matched autograft	22%	Strasberg et al., 1996
Pig	8 cm ulnar	10 mon	# Myelinated fibers	Matched autograft	~11%	Atchabahian et al., 1998a
Cynomolgus Monkey	3 cm sural allograft into ulnar defect	1 yr	Contractile force of abductor digiti quinti muscle	Sural autograft	~90%	Fish et al., 1992

~ indicates that raw numbers were not provided in the study and the shown % was calculated by estimating from the graphical representation of the data.
CMAP: Compounds muscle action potential; CsA: cyclosporine A; NAP: nerve action potential.

Table 2 | **Studies showing efficacy of temporary systemic immunosuppression with peripheral nerve allografts**

Species	Allograft length (cm)	Duration of systemic immunosuppression/ duration of study or follow-up	Treatment	Reference
Rat	2	12/30 wk	CsA	Midha et al., 1993
Rat	2	10/20 wk	CsA	Atchabahian et al., 1998b
Monkey	5	2/8 mon	FK506	Auba et al., 2006
Human	23	2/4 yr	CsA, pred	Mackinnon et al., 2001
Human	20	18/24 mon	CsA, pred	Mackinnon, 1996

CsA: Cyclosporine A; Pred: prednisone.

study in mice indicated lesser myelination for recipients of temporary immunosuppression (5 weeks immunosuppression in a 4-month study with a 6 mm PNA) (Udina et al., 2004). This study showed that all other measured metrics of histological and functional recovery showed that regeneration in recipients of temporary immunosuppression was equal or superseding that of autograft and allograft with continuous FK506.

Taking the concept of limited immunosuppression further, a more localized approach may be possible that may circumvent many of the pitfalls of systemic immunosuppression. A study showed that localized delivery of immunosuppressive regulatory T cells (Tregs) around a PNA in rats (Sprague Dawley to Lewis) using a poly(ethylene glycol) (PEG) hydrogel as the Treg delivery vehicle was sufficient to enable regeneration equivalent to the matched autograft (Santos Roballo et al., 2019). The locally-delivered Tregs infiltrated the PNA localized to host immune cells and reduced the quantity of host immune cells and did not engraft off target in the spleen.

The outcomes of full regeneration with temporary systemic immunosuppression (**Table 2**) and that of regeneration with localized Treg delivery provoke a question about how long immunosuppression must be maintained for full regeneration to occur. There are two prevailing theories on this question. The first is that immunosuppression must be maintained for the period that axons are regenerating through the PNA. While the mean rate of axon regeneration is considered to be 1 mm/d, the actual rate can vary substantially (Seddon et al., 1943). The rate of axon regeneration, however, has not been specifically quantified within PNAs but would not be likely to significantly diverge provided there was sufficient immunosuppression.

The second theory is that immunosuppression must be maintained until regenerated axons reach and functionally innervate their target tissues. The studies shown in **Table 1** may have been conducted based on this assumption because the duration of immunosuppressive therapy fits with the timeline of functional innervation of target tissues based on the location of the injuries rather than the length of the PNAs. Definitive experiments have not yet been conducted to answer this question but would be key for determining if temporary systemic or localized immunosuppression must be established based on the length of the segmental defect or on the maximum regenerative distance to innervation targets.

An additional factor that may contribute to the time that immunosuppression is required is the neurogenic potential of immunosuppressants. Calcineurin inhibitors cyclosporine and FK506 inhibit immune cell activation, but both also promote neurite extension and survival following injury (Hui et al., 2010; Saffari et al., 2019). Within neurons, calcineurin activation negatively regulates axonal extension and survival via the control of intermittent calcium waves (Lautermilch and Spitzer, 2000). Calcineurin also modulates SCs where calcineurin expression in SCs is required for proper autophagy and myelin clearance following peripheral nerve injury and promotes SC proliferation (Fansa et al., 2000; Reed et al., 2020). The direct interaction of Tregs with peripheral nerve cells has not been explored, but Tregs are potently angiogenic and known to release cytokines such as TGF-β that are separately known to directly influence neuron survival and extension (Krieglstein et al., 2002; Lužnik et al., 2020). It therefore appears that several of the immunomodulatory methods available to use with PNAs have neurotrophic and neuroprotective functions in addition to their activity as immunosuppressants.

Axon fusion is a compelling new technique that immediately reconnects severed axons after injury as opposed to the stepwise process of axon regeneration (Ghergherehchi et al., 2019). Recent studies suggest that axon fusion may be possible across segmental PN defects using PNAs without immunosuppression (Mikesh et al., 2018; Smith et al., 2020). Using outbred Sprague-Dawley rats as donors and recipients, axon fusion across a 1 cm allograft was achieved with aqueous PEG as the fusogen. Outcome measures indicated that electrical conductance was immediately restored and maintained, that fused axons remained myelinated and animals steadily regained functional control of voluntary movement over the course of the 42 days of the study. Interestingly, the degree of behavioral regeneration as assessed by the Sciatic Functional Index (SFI) was superior in the PEG-fused allograft group compared to the SFI from PEG-fused single cuts.

The function and fate of allogeneic Schwann cells

After PN injury, SCs are responsible for remodeling the environment and inducing axonal growth (Cattin and Lloyd, 2016; Klein and Martini, 2016). SCs in an injury site dedifferentiate, proliferate and migrate to form a bridge that links the nerve stumps (Cattin et al., 2015; Jessen and Mirsky, 2016). SCs produce neurotrophic cytokines which stimulate neurite survival and extension (Jessen et al., 2015; Cattin and Lloyd, 2016). Dedifferentiated SCs also help degrade myelin and recruit tissue macrophages and blood monocytes (Jessen et al., 2015; Boerboom et al., 2017; Nocera and Jacob, 2020). SCs upregulate toll-like receptors, adaptor protein myeloid differentiation primary response gene 88 and monocyte chemotactic protein 1 (Karanth et al., 2006). This leads to macrophage chemotaxis into the tissue (Barton et al., 2017). In the subsequent days to weeks after PN injury, macrophages then stimulate SCs and other immune cells to complete myelin breakdown and begin to direct axon regeneration (Barton et al., 2017).

The essential role of SCs were highlighted in a study using a mouse strain with dysfunctional SCs. SCs from the C57BL/Ola strain are impaired in myelin breakdown and consequently the process of Wallerian degeneration of cut nerves is very slow. Myelinated axons remained for more than 3 weeks after axotomy when compared to wild type (Brown et al., 1992). This slowed macrophage recruitment and phagocytosis of cellular debris, impairing regeneration. This suggests that nerve tissue distal to the injury must undergo significant remodeling in preparation for axonal regeneration, which is mediated by SCs (Brown et al., 1992).

Interesting outcomes have been noted in studies that have analyzed the fate and localization of allogeneic SCs after PN allotransplantation. In a mouse study transplanting PNs from C3H/eb Shiverer mice, which lack MBP, into BALB/c wild type found that $MBP^{+/+}$ host SCs replace $MBP^{-/-}$ SCs in the absence of immunosuppression by 6 weeks, which was the earliest time point assessed in the study (Midha et al., 1994). A rat study that assessed earlier time points using PNAs from GFP-expressing Sprague-Dawley rats implanted into Lewis rats

without any immunosuppression showed that donor SCs are still abundant 14 days after implantation and appear to form most of the regenerative bridge between donor and host nerve segments (Roballo and Bushman, 2019). Interestingly, the allogeneic SCs also migrated extensively into adjoining host PN tissue. All of this occurred despite the infiltration of host immune cells. Donor-origin SCs only began to decline in abundance between 14 and 28 days after implantation, consistent with a rise in host CD8 T cells in the grafts. However, some donor-origin SCs are still evident up to 14 weeks after implantation when there is no evidence of an ongoing immune response (Roballo and Bushman, 2019). This suggests that some allogeneic SCs evade the host immune response and have adapted to their environment which is largely composed of host-derived cells.

The previously mentioned studies on temporary immunosuppression with PNAs found that donor SCs myelinated regenerated host axons and were viable as long as immunosuppression was maintained. When immunosuppression was withdrawn, most donor-origin SCs were eliminated by the host immune response within two weeks. The process of donor SC elimination seems to be matched by replacement with host SCs in a manner that does not appear to grossly disrupt the function of regenerated axons, although more detailed study of this critical period is needed.

The fate of donor-origin SCs after PEG fusion without immunosuppression remains to be fully determined, but results suggest axonal continuity is maintained. Electrical conductance through fused axons is continuous out to the study endpoint at 42 days and TEM images at 7, 21 and 42 days shows many large diameter (> 3 μm) axons that are highly myelinated (Mikesh et al., 2018; Smith et al., 2020). The % myelin occupation temporarily decreases and myelin thins at early time points after PEG fusion, which corresponds to the times when non fusion studies suggest allogenic SCs would be eliminated (Roballo and Bushman, 2019). However, temporary myelin thinning is also observed for distal axons after PEG fusion of a single cut (Ghergherehchi et al., 2019), suggesting that myelination may be in flux in the early stages after axon fusion and temporary thinning may not necessarily be related to the immune response to a PNA.

The prolonged survival and function of allogeneic SCs without immunosuppression in axon regeneration studies and potentially axon fusion is curious because, as opposed to motor and sensory neurons which express very little MHCs (Nardo et al., 2016), non-myelinating SCs robustly express MHCs and are rapidly targeted in mixed lymphocyte type reactions (Meyer zu Hörste et al., 2010). *In vivo*, over time it is clear that the vast majority of allogeneic SCs are eliminated and replaced by host SCs, but it appears to occur over a much longer period of time than would be projected based upon the *in vitro* reactivity of SCs in mixed lymphocyte type reactions.

Infiltration and abundance of host immune cells after peripheral nerve allotransplantation

In rat PNA experiments, quantification of host immune cells showed a surprising degree of similarity in abundance and localization between the PNA without immunosuppression and autograft. For example, both groups demonstrated similar quantities of CD4 T cells at all-time points (Roballo and Bushman, 2019). The abundance of CD8 T cells was higher in autograft at 3 days, and equal between autograft and allograft at 7 and 14 days post implantation. Macrophages were higher in allografts compared to autografts at 3, 7 and 14 days. These results contrast with what have been observed for T cell and macrophages abundance in other transplanted tissues (Moreau et al., 2013; Marino et al., 2016).

A study comparing the immune reactions from autologous and xenogeneic (rat) PN grafts into mice at 2, 4 and 8 weeks without immunosuppression also suggests a more gradual immune response (Lu et al., 2009). While no functional regeneration occurred with the xenograft, it took 8 weeks for complete rejection to occur. Circulating levels of IL-2, IL-4, IFN-γ and TNF-α were elevated in xenotransplant recipients compared to autograft at 2 weeks, but this increase was modest and transient, returning to normal levels by 4 weeks, prior to the full rejection of the tissue at 8 weeks. Another study noted an upregulation of Th1-Th17-Th22 $FoxP3^+$ cells in the spleens of PN xenotransplants, suggesting a role for this subpopulation of Tregs in mediating graft rejection (Chai et al., 2014).

Potential Mechanisms

The physical barriers of the peripheral nerve

The outer layer of connective tissue surrounding a PN may play a role in the peculiar immune response (Maiuolo et al., 2019). The epineurium consists primarily of type I collagen deposited by fibroblasts, forming a dense basement membrane around the PN. The epineurium also contains the vascular supply to nerves, with endothelial cells strongly linked by many tight junctions. The connective tissue and vasculature form what is called the peripheral blood nerve barrier (BNB).

PNA experiments found that host immune cells infiltrated the graft at the donor-host boundaries, with no immune cell infiltration evident along the length of the graft (Santos Roballo et al., 2019). This pattern of immune cell infiltration suggests that BNB may limit immune infiltration after a PNA. This pattern of infiltration from the suture points rather than from all sides may contribute to the more gradual immune response to a PNA.

The BNB controls the transport of antibodies, nutrients, hormones, macromolecules and cells from the vascular system into PNs (Maiuolo et al., 2019). The BNB also regulates the immune response in PNs by restricting antibody and non-specific transcellular entry (Iwasaki, 2017; Suter and Jaworski, 2019). Consequently, infiltration of immune cells and macromolecules appears to be less permissive under basal conditions and more selective during an immune response (Iwasaki, 2017; Ruck et al., 2017).

This has not been specifically studied in the context of PNAs, but pathogen studies indicate that the BNB is selective for antigen-specific CD4 T cells. A study showed that only antigen-specific CD4 cells initially enter PNs following herpes viral infection (Iijima and Iwasaki, 2016). Once the CD4 cells with antigen specificity to the virus crossed the BNB, they stimulated wider cellular infiltration by further permeabilizing the vascular endothelium through secretion of cytokines such as IFN-γ or IL-17A in response to the infection.

Major histocompatibility complexes and antigen display

Acute rejection of allogeneic tissue is primarily mediated by MHC and mHA antigen differences, which may be altered for PNs. Baseline MHC expression in PNs is lower than that of other tissues (Trumble et al., 1994; Wolbert et al., 2020). MHC expression increases in PNA cells after transplantation, but again appears to be lower than what is observed in other transplanted tissues. Mouse studies comparing MHC expression after syngeneic or allogeneic PN implantation showed that both MHC I and MHC II increased proportional to their original levels but not as robustly of an increase as is observed in skin transplant (Trumble et al., 1994). mHA differences may also be less impactful as MHCs within PNs display fewer antigens (Bijen et al., 2018).

Unlike other tissues, rejection of PNAs appears to require incompatibility between donor and host for both class I

and class II MHCs. A study using donor skin harvested from allogeneic mice that lacked either class I or class II MHCs showed a more prolonged timeline of rejection compared to donor skin expressing both MHC classes (Trumble et al., 1994). However, complete rejection eventually occurred in skin transplants that lacked either MHC I or MHC II. In contrast, when these experiments were replicated with allogenic PNs, rejection did not occur for PNs that lacked either MHC I or MHC II.

Neurons represent one of the few classes of cells that in homeostasis express little to no MHC I and, in general, may represent a relatively immune-privileged cell population (Turnley et al., 2002; Nardo et al., 2016). Transplantation of allogenic dorsal root ganglia (DRG) neurons or SCs within a scaffold showed DRG-containing scaffolds had lower macrophage infiltration compared to the SC group (Liu et al., 2012). A study using biodegradable NeuraGen® 8 mm tubes infused with DRGs or SCs cultured from an allogeneic rat strain showed more MHC I expression in the groups that received allogenic cells when compared to sham-groups, but the DRG group caused less MHC I expression than SCs (Liu et al., 2012). Furthermore, MHC I and II expression is lower in PNAs after PEG-fusion compared to unfused PNAs (Smith et al., 2020), potentially because myelinating SCs would be expected to express less MHC than non-myelinating SCs after PNI (Lisak et al., 2016). Together, this data indicates neurons are less visible to an allogeneic immune system but also raises the intriguing possibility that functional neurons may alter the immunogenicity of the graft.

Resident antigen presenting cells

APCs are the key cell type mediating direct and indirect allorecognition. Within PNs, macrophages are the predominant APCs and there appear to be relatively few resident DCs (Roballo and Bushman, 2019). As previously discussed, macrophages play an important pro-regenerative role in injured PNs and interact extensively with SCs (Jessen et al., 2015). Macrophages within injured PNs may be more prone to promoting regeneration rather than initiating an acquired immune response (Cattin et al., 2015; Tomlinson et al., 2018). Allogeneic macrophages skew toward M2 polarization, which has lower antigen presentation capability than M1 (Cattin et al., 2015). The relative lack of passenger DCs and the propensity of macrophages to take on M2 polarization may slow host immune activation via direct allorecognition.

Endoneurial fibroblast-like cells are a recently described cell population in PNs that may have antigen-presenting capability (Richard et al., 2012; Richard et al., 2014). Endoneurial fibroblast-like cells are blood-derived mononuclear cells present in the endoneurium, are CD34-positive and express MHC II (Richard et al., 2012). They appear to be functional at MHC II antigen display, but the exact role of endoneurial fibroblast-like cells in the injury response and after allogeneic transplantation is not yet described (Muller et al., 2006).

Non-myelinating Schwann cells in lymphatic tissues

Recent studies have observed a close relationship between sensory fibers of the sympathetic nervous system with primary and secondary lymphatic tissues (Hu et al., 2018; Al-Shalan et al., 2019). The thymus and lymph nodes have sensory fibers in close physical association (Hu et al., 2018). These fibers appear to be the source of non-myelinating SCs that can be found within the thymus and lymphatic nodules under basal conditions. These SCs form an extensive meshwork inside of the thymus.

Much remains to be determined regarding the function of these SCs in lymphatic tissue. However, they are in close association with CD4 T cells, CD8 T cells and APCs (Al-Shalan et al., 2019). The known ability of SCs to express and present via MHC II (Meyer zu Hörste et al., 2010) as well as MHC I raises the interesting possibility that these non-myelinated SCs might influence central tolerance in the thymus and induction of immune cells in peripheral lymphatic tissues.

Clinical Outcomes with Peripheral Nerve Allografts and Axon Fusion

As discussed in previous sections, PNAs treated with immunosuppression showed improved recovery without rejection. In a particularly complex case, a patient with severe segmental defects to the medial and ulnar received a combination of sural autografts and allografts of medial and ulnar nerves where the allografts were separated into cables by neurolysis and stored in University of Wisconsin solution for 7 days at 5 degrees prior to implantation (Mackinnon et al., 2001). Four 37 cm allograft cables were inserted to bridge the median nerve defect, and a 15 cm gap of the ulnar nerve was bridged with four total cables, two sural autograft cables and two allograft cables. Immunosuppression with CsA, azathioprine and prednisone was initiated several days prior to implantation and continued for 12 months. Thirty-three months post-operatively, this patient showed excellent innervation of the extrinsic ulnar and median muscles, gaining light-touch sensation in the injured hand and achieving vibration thresholds of 5.7 to 10.9 in the index and ring digits respectively. Another case had similar results when the patient was treated with immunosuppression therapy a couple of days before distal digital nerve repair surgery and for at least 6 months after surgery (McKee et al., 2020).

Human clinical cases with single-cut digital nerve injuries treated with PEG-fusion using 1% methylene blue have been successfully repaired using PEG-fusion at ~24 hours post injury. That is, PEG-fusion rapidly restored sensation in singly cut human digital nerves as assessed by static 2-point discrimination and British Medical Research Council Classification (MRCC) sensory recovery score. The efficacy of PEG-fusion was evaluated in humans and retrospectively compared to recovery from standard nerve repair (Bamba et al., 2016). One study evaluated two patients (one male, one female) and the second study evaluated one female patient. All had acute traumatic lacerations involving digital nerves. Patients were treated within 24 hours of injury with PEG-fusion in conjunction with standard neurorrhaphy repair. The PEG-fused patient group was compared to six patient-matched controls treated with standard nerve repair whose data were retrospectively collected. PEG-fusion nerve repair improved outcomes and speed of nerve recovery in the clinical setting as assessed by average MRCC score in 1 week (2.8 *vs*. 1.0, $P = 0.03$). At 4 weeks, MRCC scores remained superior in the PEG-fusion group (3.8 *vs*. 1.3, $P = 0.01$). At 8 weeks, there was improvement in both groups with the PEG-fusion cohort remaining statistically better (4.0 *vs*. 1.7, $P = 0.01$). We note that the time course and extent of the clinical recovery of two-point discrimination is similar to that reported for SFI behavioral recovery in rats when both are plotted on the same graph (Bamba et al., 2016).

Conclusion

While it is well known that the central nervous system has a degree of immunological privilege, an increasing body of evidence indicates that the peripheral nervous system is also immunologically peculiar. These peculiarities are particularly evident after allogeneic PN transplantation where the host immune response is both more gradual and less severe than what is observed for other transplanted tissues. These differences are likely due to functional differences for PNAs, as a temporary scaffold for regeneration of host axons, as well as intrinsic immunological differences from many other transplanted tissues. Further research identifying the

mechanisms responsible for these peculiarities would be beneficial for PN regeneration and the field of transplantation.

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