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Review

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The neurobiology of targeted muscle reinnervation for post-amputation pain

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Abstract

Targeted muscle reinnervation (TMR) is a peripheral nerve procedure that can prevent and treat postamputation pain. The nerve transfer allows for organized nerve regeneration and repair after amputation surgery. The procedure can successfully prevent neuromas despite large size mismatches between the donor and recipient nerves. Here, we discuss the fundamentals of peripheral nerve injury and regeneration as it pertains to TMR. We propose axonal pruning to explain axon behavior when there are large size mismatches between transferred nerves. Given the increasing use of TMR for amputees, future studies should investigate the basic science of peripheral nerves in TMR. Advances in this field have the potential to significantly improve clinical outcomes for these patients.

Keywords: Targeted muscle reinnervation, peripheral nerve injury, nerve regeneration, axonal pruning

INTRODUCTION

More than 2 million amputees live in the United States, and approximately 185,000 amputations occur in the United States each year[1]. Pain is a significant problem affecting more than 70% of amputees[2]. Peripheral nerve injury and subsequent improper axon regeneration result in a disorganized bundle of nerve tissue, known as a neuroma[3]. Neuromas are a known cause of postamputation pain, which includes

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residual limb pain (RLP), phantom limb sensations (PLS), and phantom limb pain (PLP)[3]. RLP is pain at the site where amputation occurred, often due to nerve injury and neuroma formation[3]. PLS are non-painful sensations in the amputated limb, which may lead to PLP[3]. Meanwhile, PLP represents neuropathic pain localized to the lost limb[3]. Postamputation pain contains significant overlap, and patients with neuromas are significantly more likely to suffer from PLS and PLP[4,5]. Postamputation pain has a significant impact on patient outcomes, including prosthetic use, return to work, and overall quality of life[6].

Unfortunately, postamputation pain is complex and poorly understood, and treatment of postamputation pain remains difficult[4,7]. Targeted muscle reinnervation (TMR) is an emerging surgical procedure to manage nerves and treat pain in amputees. TMR involves transferring the proximal stump of transected major peripheral nerves to nearby motor nerves of muscles that lack function after amputation[8]. In surgery, the major peripheral nerve being managed with TMR is identified, dissected, and cut distally to healthy fascicles. The recipient motor nerve is identified using a nerve stimulator and cut just proximally to any areas of branching into muscle. The small recipient motor nerve is sutured to the center of the large donor nerve in an end-to-end fashion. Fibrin glue is used to reinforce the coaptation and prevent collateral axonal sprouting and neuroma formation. TMR was originally performed by Kuiken *et al.* in 2004 to improve myoelectric prosthetic control[9]. Incidentally, TMR was found to successfully treat and prevent neuroma pain in amputees, sparking an explosion of new research into TMR[4,7]. Recent literature shows the clinical success of TMR, the expansion of its use, and improvements in surgical technique[4,5,8]. However, there is a paucity of literature exploring the basic science of nerve regeneration pertaining to TMR and how the procedure actually prevents neuroma formation. Surprisingly, the procedure can be successful in preventing neuromata despite a large size discrepancy between donor and recipient nerves[4,10]. No known studies have explained a possible mechanism for axon behavior when there is a large size mismatch between transferred nerves. The purpose of this review is to attempt to explain the process of nerve regeneration in TMR for postamputation pain and to propose axonal pruning as a potential mechanism for axon behavior in the setting of a large size mismatch between coapted nerves.

PERIPHERAL NERVE ANATOMY

The main functions of the PNS are to send sensory information to the CNS, transmit motor commands to voluntary striated muscles in the body, and regulate autonomic functions such as blood pressure[11]. Therefore, the PNS contains motor, sensory, and autonomic nerve fibers that combine to form motor, sensory, or mixed nerves[11,12].

The PNS is myelinated by Schwann cells that increase the speed of action potential propagation[11]. Schwann cells are the supporting cells of the PNS that surround and protect axons[13]. In addition to myelin, peripheral nerves are surrounded by three well-organized connective tissue layers: endoneurium, perineurium, and epineurium[11] [Figure 1]. The endoneurium is the innermost compartment surrounding individual nerve fibers, and it forms the blood-nerve barrier[13]. The nerve fibers are grouped into fascicles, which are enveloped by concentrically arranged perineurium[13]. The epineurium is the outermost layer of peripheral nerves, containing several nerve fascicles and the nerve's blood supply[13]. The well-organized peripheral nerves and their tissue are essential for proper neurotransmission, as well as normal nerve regeneration following peripheral nerve injury.

PERIPHERAL NERVE INJURY

Peripheral nerve injury (PNI) can have a significant impact on a patient's quality of life[15]. PNI frequently develops into neuropathic pain, which is a complex form of pain that is modulated by both the PNS and CNS[15,16]. Sunderland *et al.* were the first to classify peripheral nerve injuries and offer a prognosis for nerve

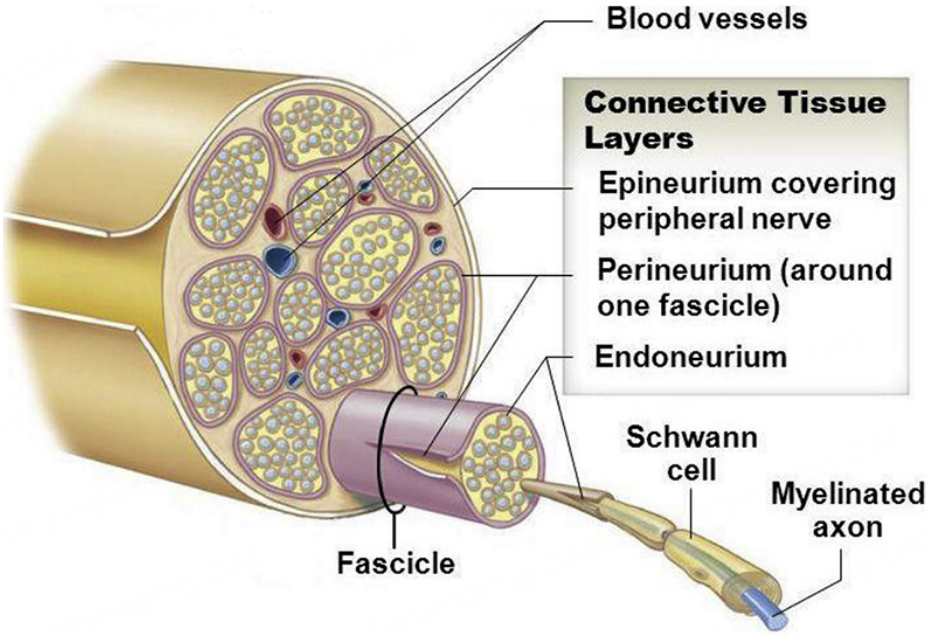

Figure 1. Schematic presentation of a peripheral nerve. Source: Nicholls *et al.*[14].

repair based on the degree of connective tissue disruption[16] [Figure 2].

Since mature neurons are terminally differentiated cells that are incapable of mitosis, a nerve injury to the cell body cannot be repaired and results in apoptosis[13]. However, there are two main mechanisms for axonal regeneration: terminal sprouting from injured axons and collateral axonal branching from intact axons[13,18,19]. This is largely because Schwann cells, unlike neurons, can undergo mitosis if injured[13]. Understanding the fundamentals of peripheral nerve degeneration and regeneration after injury will help inform targeted muscle reinnervation for the treatment of postamputation pain.

In limb amputation, peripheral nerve injury is unavoidable[8,20]. Amputation requires nerve transection and can be considered a Sunderland grade 5 nerve injury, in which all connective tissue layers are disrupted and the distal target for nerve regeneration is removed[16] [Figure 2]. Injury begins the peripheral nerve degeneration cascade. Within hours, degeneration of the axon and myelin begins in both directions from the site of injury in a complex process known as Wallerian degeneration[13]. Wallerian degeneration is the rapid, vigorous process of degeneration of distal and some proximal segments of axon after nerve injury[13,17] [Figure 3]. The disruption of the axon plasma membrane causes the influx of extracellular calcium ions, which triggers proteolysis, fragmentation, and degradation of the myelin and axons[21]. Schwann cells dissociate from the axon and transition into repair cells to help digest myelin[21]. Schwann cells initially phagocytose debris before the macrophages are recruited and enter through the leaky blood-nerve barrier[21]. Macrophages are critical to Wallerian degeneration as they rapidly engulf and digest debris, clearing the path for nerve regeneration to occur[17,21]. Wallerian degeneration begins within 24 h of injury and completes after 3 weeks[22].

Wallerian degeneration traditionally refers to the degeneration of distal detached axon segments after nerve injury but has also been found to extend proximally from the site of injury[13]. Wallerian degeneration proceeds proximally for about two internodes before the axon is sealed within hours of injury[13]. This is thought to protect the intact axon and cell body from the extracellular environment and apoptosis while

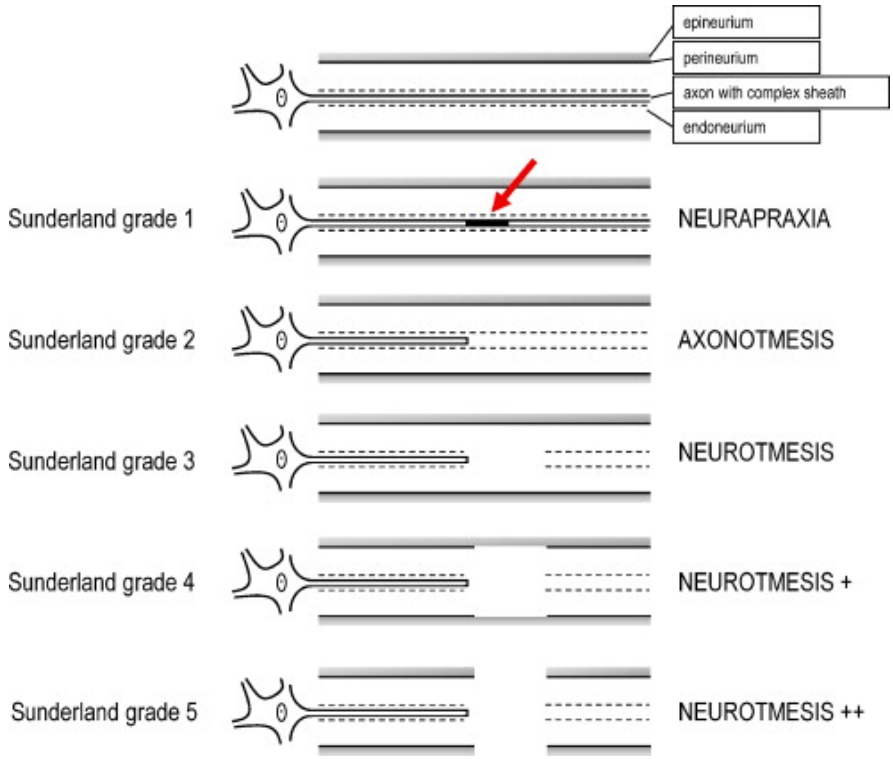

Figure 2. Sunderland peripheral nerve injury classification. Source: Deumens *et al.*[17].

allowing retrograde chromatolysis to proceed[13,22].

The chromatolytic changes seen in PNI include disintegration of Nissl bodies (cisterns of the rough endoplasmic reticulum) in the cytoplasm, an eccentric nucleus, a prominent nucleolus, and an increase in RNA and protein synthesis[17]. In peripheral nerve injury, these chromatolytic changes reflect a shift of metabolic activity away from the synthesis of proteins for neurotransmission and towards proteins required for growth and axon sprouting[17]. Depending on the environment and degree of injury, retrograde chromatolysis may cause the neuron to produce apoptotic proteins, in which case nerve regeneration fails and the neuron undergoes programmed cell death[17]. If the neuron survives, the retrograde reaction peaks at 2-3 weeks after the nerve injury[13,17]. In this instance, nerve degeneration quickly transitions to nerve regeneration[17].

PERIPHERAL NERVE REGENERATION

Nerve regeneration begins when Schwann cells undergo mitosis and rapidly proliferate[17] [Figure 3]. After assisting with the initial degradation of the injured axon and myelin, Schwann cells align from both ends of the damaged nerve to form new endoneurial tubes across the injury site[17]. These are known as bands of Bü ngner, through which new axon sprouts can grow[17].

Once retrograde chromatolysis has peaked, regenerative terminal sprouting and collateral axonal branching can begin[17-19]. Axon sprouts grow along the bands of Büngner at an average rate of 1-3 mm/day towards their distal targets[17]. Distal nerve stumps and target tissues have attractive forces on axon sprouts that likely drive chemotaxis[17]. Since axon sprouting and growth cones require an organized endoneurial tube, the extent of endoneurial tube disruptions during injury determines the healthy regeneration of the nerve axons

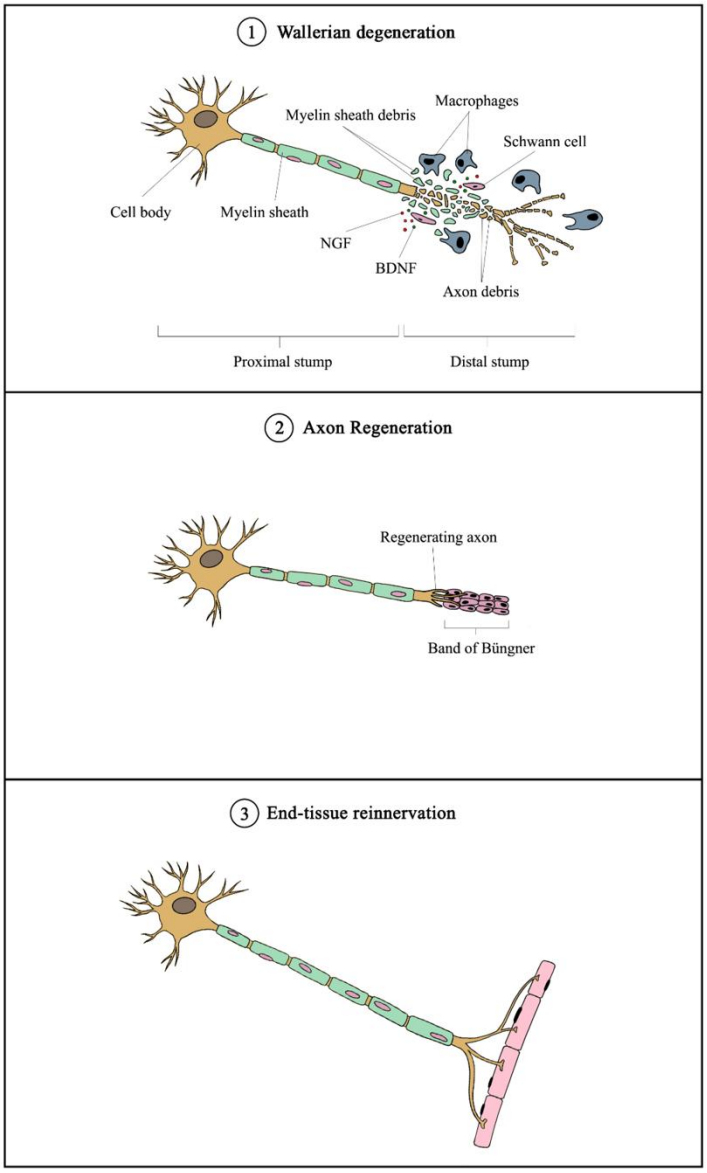

Figure 3. Overview of the mechanism of peripheral nerve injury and regeneration. Source: Yow *et al.*[23].

to their intended targets[16]. Depending on the distance the axon sprouts must travel, sprouts may take weeks to months to traverse the axon injury gap and re-enter appropriate endoneurial tubes[24]. Eventually, the axon sprouts extend through the distal target nerve with support from Schwann cells in the bands of Büngner[24].

Collateral axonal branching occurs via a different mechanism[18,19]. The de novo branches stem from the main axon of the injured neuron or from the axons of nearby uninjured neurons[18]. The outgrowths are formed by actin filament protrusions that become invaded by stable microtubules[18]. The microtubules allow the branches to mature and continue extending toward their target[18]. Collateral branches enter Schwann cell tubes, which guide reinnervation to their target in a similar way to terminal sprouting[25].

Successful nerve regeneration is established when neurotransmission through the injured neuron is restored[17,21]. Axon sprouts that successfully enter the distal target will become re-myelinated and grow stronger with use[13]. Once regeneration is complete, chromatolysis is reversed and cell function returns to normal[17].

NEUROMA FORMATION/FAILURE OF REGENERATION

Nerve regeneration can fail at any step in this process[17]. If the cell body is injured, retrograde chromatolysis may result in the production of apoptotic proteins and cell death[17,26]. If regenerative axon sprouts fail to cross the injury site due to large gaps, a physical barrier formed by scarring, or other factors, the axon sprouts will form a neuroma[17]. Aberrant sprouting may occur in limb amputation when nerves are not given a new target[10]. Neuromas are a common cause of postamputation pain and may negatively impact the function and quality of life of amputees[3,4].

Collateral axonal branching is frequently misdirected and can cause improper innervation of distal targets[27,28]. For instance, nearby sensory nerves can branch to reinnervate the distribution of an injured or cut motor neuron[27,28]. This can produce painful hyperalgesia that is often misinterpreted as neuroma pain[28]. The hyperalgesia due to the collateral branching of sensory axons produces a burning sensation and hypersensitivity to touch[28]. However, collateral branching does not contribute to neuroma formation and is not amenable to surgery. It can be treated with desensitization therapy[28].

PHANTOM LIMB SENSATIONS AND PAIN

PLS are any non-painful sensations that occur in the missing body part after amputation[29,30]. Over 90% of amputees experience PLS in the first 6 months[30]. Phantom sensations may include feelings of movement, touch, tingling, itching, or paresthesia in the missing limb[31].

The causes of phantom sensations are not well understood and are thought to involve both peripheral and central mechanisms. After amputation surgery, neuroma formation and abnormal spontaneous neuronal activity at the proximal end of the cut peripheral nerves may contribute to phantom sensations[32,33]. Neuromata have been shown to correlate with increased duration and intensity of phantom sensations and phantom limb pain[33]. Also, injured peripheral nerves have upregulated sodium channels, causing increased sensitivity to mechanical stimulation and abnormal firing[32,33]. The increased sensitivity of the injured nerves decreases the pressure pain threshold, which may explain why some amputees experience increased PLS and PLP with prosthetic use[32,33].

PLS are also thought to be modulated via central mechanisms. The somatosensory homunculus in the cortex of the brain receives sensory, positional, and movement information from peripheral nerves[34]. The cortical representation of an amputated limb likely persists for some time after limb amputation resulting in a phantom limb[34]. Reorganization of the somatosensory cortex may also underlie phantom sensations[35]. Neurons in the somatosensory cortex that previously responded to signals from the missing limb can begin to respond to signals from other nearby neurons[35]. As a result, stimulation of nerves in other parts of the body can be aberrantly received by the neurons of the amputated limb in the somatosensory cortex, causing sensations to be improperly perceived[35]. Phantom limbs usually change and fade over time, and most PLS disappear after 2 to 3 years[4]. However, PLS may become painful and develop into phantom limb pain in about 45% of patients[34,36].

Phantom limb pain is a complex interplay between neuromas and the central nervous system. PLP is a type of neuropathic pain that can include burning, throbbing, crushing, cramping, or sharp pain in the missing limb[36]. Cortical reorganization is a key component of PLP, and it is even more difficult than neuroma pain to prevent or reverse[4]. Therefore, treating neuromas may prevent cortical reorganization and further centralization of PLP[4,34]. In a prospective, multicenter, randomized clinical trial, Dumanian *et al.* found evidence that TMR significantly decreases phantom pain in major limb amputees compared to standard treatment at 1 year[4]. Therefore, TMR may prevent PLS and PLP by addressing the contribution of peripheral nerve injury to these experiences.

SIZE MISMATCH AND AXONAL PRUNING

TMR often involves a size mismatch between the donor and recipient nerves at the nerve coaptation site[37] [Figure 4]. The ideal nerve coaptation is a 1:1 diameter ratio and the recommended size ratio is less than 2:1[20]. However, the current practice is to accept large size mismatches in TMR[37]. Depending on the available anatomy, the physiological and clinical implications of the size mismatch are unknown, but Kim *et al.* and Dumanian *et al.* found that patients having TMR did not develop symptomatic neuromas at nerve coaptation sites despite large size mismatches[4,10]. No prior works have addressed why TMR is successful despite large size mismatches between the donor and recipient nerves. Kim *et al.* posited that there is likely a critical mass effect where TMR is successful after enough targets are provided for the regenerating nerve sprouts[10]. However, this does not explain what comes of the growing nerve sprouts that fail to reach their targets.

A possible theory to explain why TMR works despite a large size discrepancy between transferred nerves is the process of axonal pruning. Axonal pruning is selective axon degeneration that removes unnecessary, misguided, or excessive axon sprouts while maintaining the integrity of the cell body[26,38,39] [Figure 5]. Singh *et al.* showed that during axon competition, active (i.e., winning) axons can eliminate less active, competing axons by axonal pruning[40]. Axonal pruning is well established in the development of the CNS and PNS[26,40]. Selective degradation of axons that unsuccessfully innervate their targets or are no longer necessary allows for optimal wiring of neural connections in the developing nervous system[26].

Axonal pruning has previously been described in the context of nerve injury. Following an injury to a mixed peripheral nerve, regenerating motor axons will preferentially enter both sensory and motor Schwann cell tubes over regenerating sensory axons[42]. The preferential motor reinnervation of distal targets - known as preferential motor reinnervation (PMR) - is made possible by the pruning of sensory axon sprouts while maintaining motor axons[27,42] [Figure 6]. We believe axonal pruning may explain the elimination of misguided axonal sprouting in TMR, allowing for successful reinnervation despite large size mismatches between the donor and recipient nerves.

Axonal pruning is distinct from Wallerian degeneration and neuronal apoptosis, although all three processes result in axon degeneration[26]. A key feature of axonal pruning is the selective, controlled degradation of axon fibers without inflammation or damage to the cell body[26]. As previously described, Wallerian degeneration is an inflammatory reaction that occurs in response to nerve injury[17], while apoptosis is the programmed death of the entire neuron, including the axon and cell body[26]. The apoptosis pathway is highly restricted after development as neurons cannot regenerate[44]. Axonal pruning, however, is critical to adult neural plasticity, as it permits the selective loss of specific axon sprouts while maintaining nearby axon segments and the integrity of the cell body[26]. Therefore, axonal pruning is the most likely mechanism to explain the behavior of axon sprouts at nerve coaptation sites in TMR.

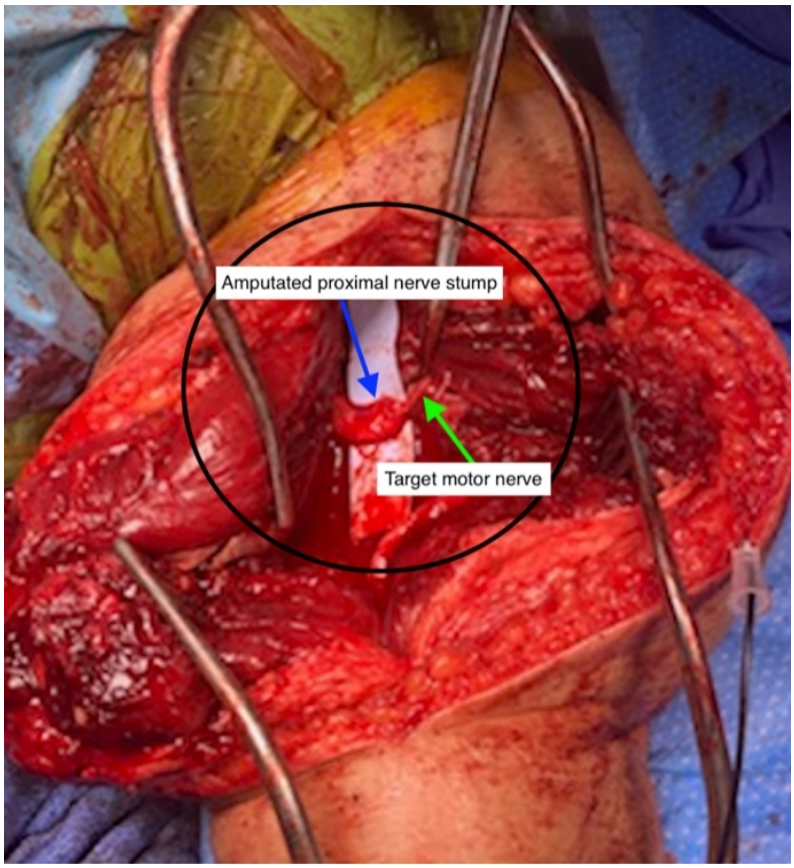

Figure 4. Size mismatch between transferred nerves in TMR.

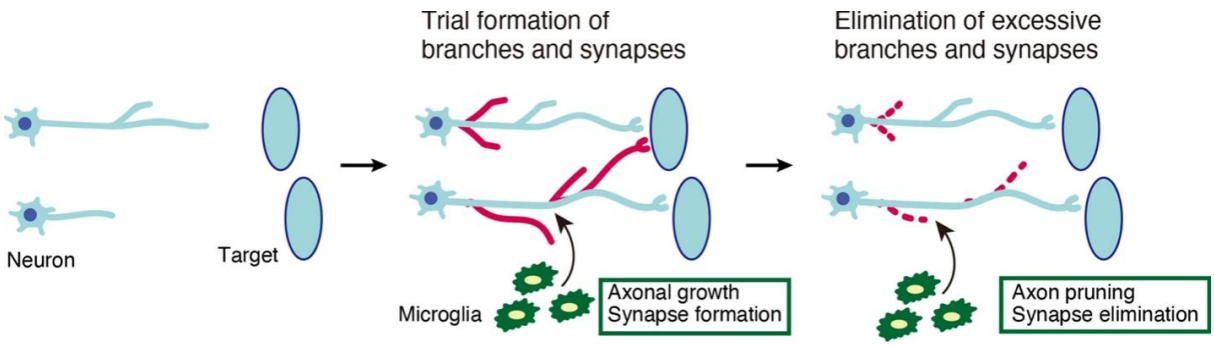

Figure 5. Schematic model illustrating axonal pruning for refining neural connections. Source: Fujita *et al.*[41].

DISCUSSION

Targeted muscle reinnervation is a major surgical advancement in the field of amputation surgery. Since its introduction in 2004, the use of TMR has been growing rapidly with the main goals of treating and preventing painful neuromas and improving the function of amputees. There has been an abundance of research into the clinical success of TMR and its growing indications for use. However, there is a gap in the basic scientific descriptions of peripheral nerve behavior in TMR. Our review aims to fill this gap and provide a better understanding of neurobiology as it pertains to TMR.

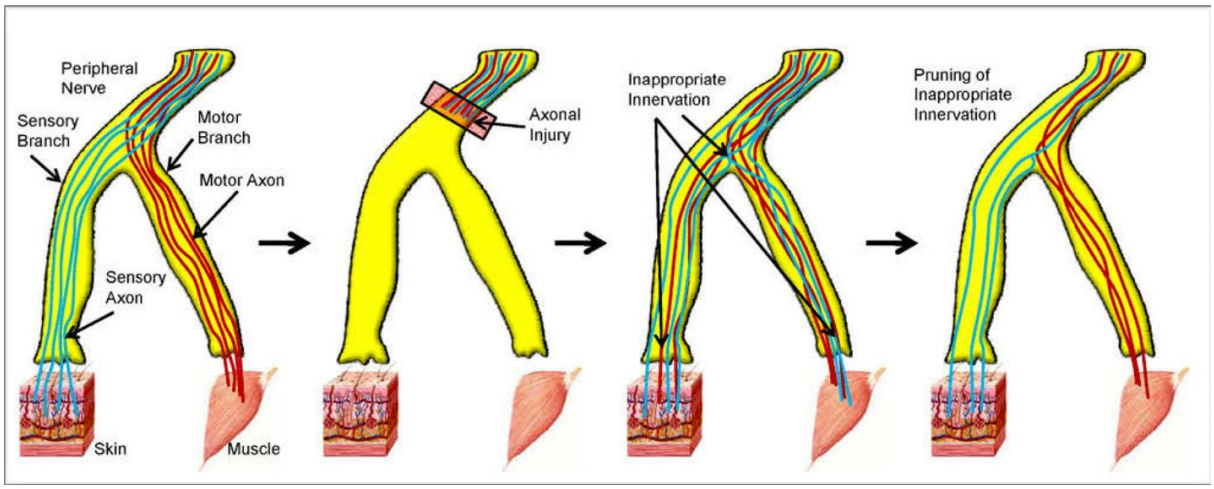

Figure 6. Preferential motor reinnervation. Following an injury to a mixed peripheral nerve, regenerating axons will preferentially reinnervate modality-matched targets driven by target signals. Regenerating axons that inappropriately innervate mismatched sensory or muscle targets undergo axonal pruning. Source: Mackinnon *et al.*[43].

Injured peripheral nerves will always attempt to reach a distal target after injury. Amputation surgery requires the transection of nerves and eliminates a distal target for organized regeneration, creating a high-risk environment for neuroma formation[4,8]. TMR provides a physiologically appropriate environment for regenerating axons and establishes a new distal target, thus preventing neuroma formation. Advances in the understanding of peripheral nervous system pathophysiology can further improve TMR techniques and treatment for patients.

Based on the principles of peripheral nerve injury and regeneration, it is surprising that several clinical studies have found that TMR can successfully prevent neuromas despite large size mismatches between the transferred nerves[4,8]. This is unexpected given the many sprouting axons from the larger proximal peripheral nerve stump that are left without organized connective tissue or a distal target to guide normal regeneration. Here, we propose axonal pruning as a viable explanation for the process of eliminating misguided or unnecessary sprouts when there is a significant size mismatch between transferred nerves in TMR. Axonal pruning may explain why TMR prevents neuroma formation and allows an optimal highway to the new target to form. However, no studies have been performed to support this theory, and further study is necessary to determine the mechanism preventing neuroma formation when there is a large size mismatch between the transferred nerves in TMR.

There are several limitations to this review since the mechanisms behind TMR and postamputation pain are complex and have not been extensively studied. The information in this review was drawn from a diverse set of orthopedic, neurobiology, and pain studies to better understand the behavior of peripheral nerves in TMR. There is a strong need for basic scientific models of TMR and further investigation in this field. It is our hope to trigger future research to further identify the pathways through which TMR can be clinically effective.

TMR can be considered by surgeons performing amputations and for other indications such as neuroma management. Clinical practice momentum is shifting towards routinely offering TMR at the time of primary amputation. However, before recommending this widespread change in clinical practice, comprehensive high-level evidence to support this practice is needed. In this review, we attempt to bridge

the gap between the literature on the peripheral nervous system and TMR.

CONCLUSION

In conclusion, TMR can be successful in treating neuromata and postamputation pain in amputees. Given the increasing use of TMR for amputees, further research should be done into the basic science of TMR. A better understanding of the mechanism of peripheral nerve injury can help surgeons improve treatments for amputation patients and develop new surgical techniques to prevent pain. Comprehensive, evidence-based knowledge of TMR has the potential to vastly improve the outcomes, function, and quality of life of amputees.

DECLARATIONS

Authors' contributions

Made substantial contributions to the conception and design of the study, implementation of the research and interpretation: Tanner N, Ayalon O

Took the lead in writing the manuscript with input and critical feedback: Ayalon O, Tanner N

Discussed the findings and contributed to the final manuscript: Tanner N, Ayalon O

Availability of data and materials

Not applicable.

Financial support and sponsorship

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Conflicts of interest

Both authors have declared that there are no conflicts of interest.

Ethical approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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