REVIEW

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Peripheral nerve injury and its regeneration processes: a biomolecular point of view

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ABSTRACT

Peripheral nerve regeneration occurs spontaneously after injury due to the permissive environment and activation of the intrinsic growth capacity of neurons. Injuries can be divided into three categories: neurapraxia, axonotmesis and neurotmesis. Wallerian degeneration occurs due to axonotmesis and neurotmesis, affecting the axon distal to the site of damage. After this phase is complete, the damaged neurons try to rebuild the damaged fibers with axonal budding. Axonal growth can occur efficiently, which is influenced by signaling molecules and the integrity of the connective tissue tunnel. It can allow axons to grow back in the right direction and innervate the innervation of the target tissue.

Keywords: nerve, peripheral, injury, regeneration processes, biomolecular.
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INTRODUCTION

Peripheral nerve injuries (PNI) are common, occurring in 2.8% of patients with trauma and sometimes affecting young and otherwise healthy people.[1] Peripheral nerve injury can result in loss of autonomic nerve function. In addition, apraxia and pain that lasts a long time is a disorder that can change a person's quality of life which varies from various levels of movement and sensation disability.[2] The common causes of PNI are traumatic conditions, surgery and certain diseases like cancer and diabetes. However, trauma-associated PNI can increase the social and economic burden of young adults.[3]

Immediately after injury, peripheral nerves can regenerate. A series of biomolecular events occurs in the cell body, proximal segment and distal nerve segment. Chromatolysis, axonal sprouting, Wallerian degeneration and formation of a band of Büngner are various biomolecular events that allow axon regrowth in the right direction and reinnervation of the target tissue. Schwann cells (SC), which are the primary glial cells of the peripheral nervous system, act as orchestrators; and there are many cells involved, such as macrophages, satellite glial cells, and fibroblasts. These biomolecular events provide a permissive microenvironment for the regeneration process and activate the intrinsic regenerative ability of the peripheral nervous system.[1–3] This article reviews topics related to the nervous system's anatomy and innate processes associated with natural tissue regeneration attempts.

Peripheral Nerve Anatomy

All nerves and associated ganglia originate in the brain and spinal cord, making up the peripheral nervous system. When nerve fibers extend from the brain, they are called cranial nerves, and when they extend from the spinal cord, they are called spinal nerves. Both cranial and spinal nerves are composed of nerve fibers and support connective tissue by forming nerve bundles (Figure 1).[4]

The connective tissue that supports nerve cells has a dual purpose in serving the nerve cells. First, connective tissue can provide mechanical protection by preventing stress and compression of nerve fibers during body movement. Second, it provides nerve fibers for trophic support in blood vessels (vasa nervorum). Three layers together with connective tissue make up the peripheral nerve fibres, namely the epineurium, perineurium, and endoneurium, arranged from the outermost layer to the innermost layer.[4] Table 1 summarizes the constituents and functions of the three layers.

Neurons are the primary cells that make up the peripheral nervous system. Neurons are supported by other cells such as Schwann cells, macrophage cells, and satellite glial cells that will together play a role in axon regeneration according to their respective roles.[5] Schwann cells function to create supportive environmental conditions by producing extracellular matrix, cell adhesion molecules, integrins, and neurotrophins.[6] The role of phagocytosis, both phagocytosis of nerve fibers and decomposed myelin in the peripheral nervous system, is carried out by macrophage

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cells.[7] Satellite glial cells regulate the external chemical environment.[8]

PERIPHERAL NERVE INJURY

Sir Herbert Seddon, in 1943, defined and classified three basic types of nerve injury based on the mild/moderate/severe surgical model, namely, neuropraxia, axonotmesis, and neurotmesis. First-degree injuries, namely neuropraxia, are the most common injuries caused by blunt trauma. The resulting condition is a temporary conduction block with demyelination at the site of injury. Sensory dysfunction is a clinical symptom of neuropraxia, when the examination found the loss of Tinel's sign and electrophysiology was negative. The condition of neuropraxia can recover by taking a few days or up to 12 weeks for healing time. Axonotmesis is a second-degree injury in which axonal failure occurs, but the connective tissue layer is preserved. Trophic growth factors and survival factors for axons and nerve cell bodies are released by peripheral nerves distal to the site of injury, where they trigger the formation of proximal axonal buds. In addition, there are also chemotactic variables that are released from distal peripheral nerves and help direct the direction of axon growth.[9]

Clinically, motor and/or sensory dysfunction was noted, and a positive Tinel's sign was found at the injury site. Decreased nerve conduction velocity and increased regional muscle denervation with fibrillation can be found on electrophysiological examination. A third-degree injury, neurotmesis, is the most significant injury in which the nerve cells are physically separated. Electrophysiological tests found no activity until surgery was performed. Electrophysiological tests cannot differentiate axonotmesis from neurotmesis. This classification of nerve injuries is easy to understand and commonly used among electrophysiologists. However, important nerve injuries are also further differentiated based on differential involvement of the neural layer according to a surgical perspective and based on potential nerve recovery.[4,10,11]

Sir Sydney Sunderland then identified five degrees of peripheral nerve injury, namely, neuropraxia as a first-degree injury, axonotmesis as a second-degree injury, and third, fourth, and fifth-degree injuries, respectively, namely damage to the endoneurial tube, perineurium, and epineurium.[12] In the third, fourth, and fifth damage, the connective tissue sheath breaks, so there is a possibility that the sensory endings and the muscle endplates are not re-innervated and the healing pattern based on the capacity of the muscle unit is usually mixed and often incomplete. In third-degree injuries, fascicular continuity persists, and retrograde degeneration is more common than in second-degree injuries. Conservative management may take several months to heal. Surgical intervention is required to remove the trap site with or without minimal neurolysis of the swollen nerve. Internal bleeding and fibrous tissue in fourth-degree nerve injury can inhibit the regeneration of guided nerve endings, resulting in neuroma-in-continuity. Full nerve discontinuities and end-bulb neuroma developmental discontinuities are classified as fifth-degree injuries. In both fourth and fifth-degree injuries, Tinel's sign and muscle unit capacity were not observed. The electrophysiological examination was unable to differentiate between fourth and fifth-degree injuries. Functional recovery at both levels of injury is difficult to expect if surgical intervention is not performed. In the continuity of the

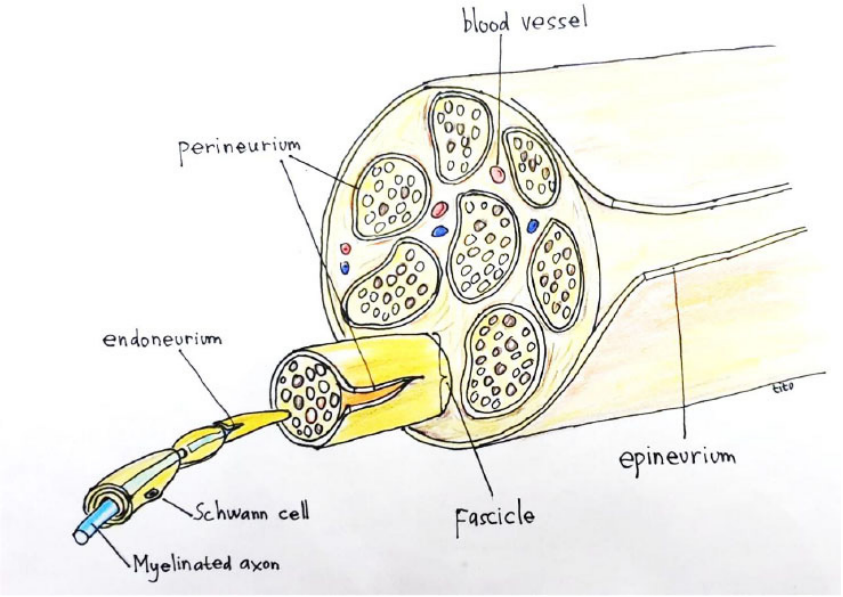

Figure 1. Peripheral nerve anatomy. The peripheral nerve consists of epineurium, perineurium, and endoneurium, covered as layers from outermost to innermost. The Schwann cells cover the axon in the endoneurium channel.

Table 1. Constituents and functions of the layers of a peripheral nerve.

Layer	Constituents	Functions
Endoneurium (innermost)	Loose collagenous matrix, nerve fibers, Schwann cells, fibroblasts, endothelial-like cells, macrophages and mastocytes	Provides further protection from mechanical force
Perineurium	Epithelium-like cells and collagen fibers	Encloses the fascicles and provide a mechanically strong protection for them
Epineurium (outermost)	Blood vessels	Ensheaths the nerve and isolates it from the external environment

Table 2. Nerve injury classification.

Sunderland	Seddon	Features
Type 1	Neuropraxia	Damage to local myelin only
Type 2	Axonotmesis	Division of intraneural axons only
Type 3	Axonotmesis	Division of axons and endoneurium
Type 4	Axonotmesis	Division of axons, endo- and perineurium
Type 5	Neurotmesis	Complete division of all elements including epineurium
Type 6*	Mixed	Combination of types 1–5

**Mackinnon modification of Sunderland's criteria and is a common clinical scenario.*

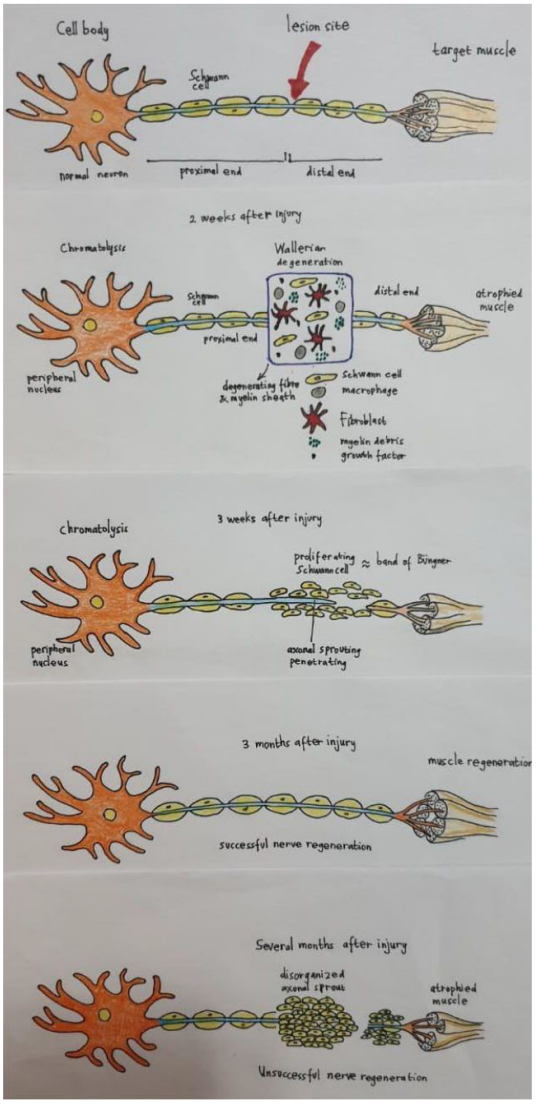

Figure 2. The processes of nerve degeneration and regeneration are related to the cellular response to nerve injury. Wallerian degeneration begins with a traumatic injury to an axon with Schwann cells that envelop myelin. The distal axon will undergo proliferation and cellular changes. Macrophages and Schwann cells at the lesion site will change to a pro-regenerative phenotype that will collect debris from destroyed axons and myelin. Büngner bands provide a permissive growth environment for axons to reach the distal target to function properly. Without Büngner's band, it causes irregular shoot growth, so that nerve regeneration fails.

neuroma, there may be focal or diffuse fibrosis. However, action potentials can be generated by stimulation between uninjured nerves with minimal segment involvement and muscle contraction. Internal neurolysis with careful dissection can improve nerve regeneration but contributes to increased scarring. Opportunities for functional regeneration in the absence of nerve conduction can be obtained through neuroma resection and grafting of the injured nerve. Nerve transfer can maximize injury recovery if excessive duration or slow regeneration of the neural cleft after grafting. The epineural or perineural sutures connecting the proximal and distal nerve endings can be secured with fibrin glue. This procedure is an option for distal nerve repair and can avoid stress co-application.[13,14]

Mackinnon and Dellon added a mixed form of fourth-degree injury to the Sunderland classification.[15] This classification describes injuries that are not associated with the conventional inside-out model (Sunderland's classification) but may include different layer types on the cross-section of the nerve. In general, direct nerve injury can result from penetrating trauma and fracture/dislocation. Recovery from nerve injury depends on the degree of injury (I-V), the presence of neurolysis, nerve transplantation, or nerve transfer.[16] Table 2 presents the definition of classification of nerve injury by Seddon and Sunderland.

WALLERIAN DEGENERATION

The peripheral nerve healing process involves various events in successive phases with different rates between the proximal and distal ends at the injury site (Figure 2).[17,18] Chromatolysis is the process of degeneration of the axon and cell body at the proximal end through programmed cell death pathways.[19] Within 24-48 hours after injury, Wallerian degeneration occurs at the distal end involving all components of the nerve, including the axon and myelin.[20] This phenomenon occurs to clear the remnants of debris from the axonal and myelin, which will be phagocytosed by Schwann cells until the endoneurial tube remains.[5]

After phagocytosis of debris, Schwann cells will fill endoneurial tubes, which

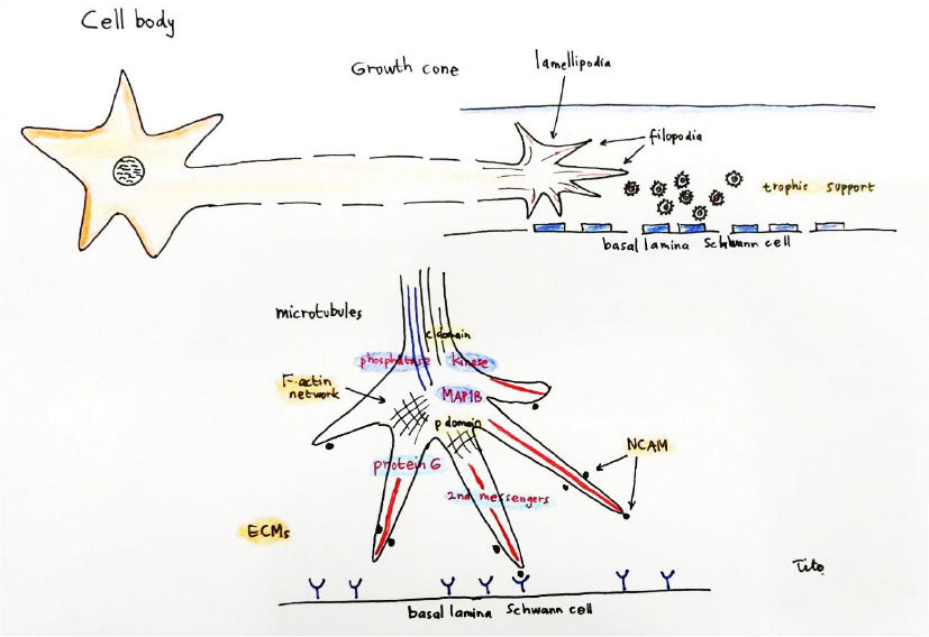

Figure 3. Lamellipodia and filopodia communicate with the adjacent matrix during neurite extension.

will become Büngner characteristic bands or tubes. Schwann cells play an essential role, promoting the growth of regenerated axons by recruiting macrophages to release growth factors and cytokines. Axonal regeneration will start from the growth cone at the tip of the proximal injury, which will grow following the guide of Büngner's band (Figure 3).[10] The process of axonal regeneration is prolonged at a rate of 1 mm/day under ideal conditions, so muscle reinnervation and functional recovery can take as little as one year.[5,14]

Nerve fibers distal to the type of axonotmesis and neurotmesis injury will lose contact with the nerve cell body to reduce the supply of protein, glycoprotein, lipid, and carbohydrate synthesis sources.[21–23] This triggers Wallerian degeneration, in which Schwann cells will form a connective tissue sheath and the basal lamina tube.[24] The action potential is maintained by sustaining the capacity of axonal transport in the proximo-distal direction up to two days post-injury.[25] Direct imaging of calcium shows an early calcium influx localized to the axotomy area with waves in the cytoplasm and mitochondria of the distal nerve.[1,26,27] Calcium will induce endogenous proteolysis and degeneration of the axonal cytoskeleton. Schwann cells will phagocytose axons and myelin, resulting in fragmentation until disintegration.[19]

The interleukin-1 (IL-1) plays an essential role in both initiation and control processes in the infection and injury process. The interleukin-1 (IL-1) family of cytokines consists of 11 members, of which IL-1, IL-1β, IL-1 receptor antagonist (IL-1RA), IL-18, and IL-333 have been well studied.[28] IL-1R1 and IL-1β are expressed in the central nervous system, affecting glial cells, endothelial cells (EC), and neurons. IL-1β can be elevated due to astrogliosis (eg astrocyte proliferation) and astrocytic release of glutamate, nitric oxide (NO), potassium, prostaglandins (PG), cytokines, and chemokines, and high concentrations are toxic to neurons. IL-1β expression is regulated through 1400 genes in astrocytes. IL-1β can activate microglia to express pro-inflammatory mediators such as prostaglandin E2 (PGE2), cytokines, and chemokines. Microglia can also express IL-1β, which can activate astrocytes in the mouse brain to develop ciliary neurotrophic factor (CNTF) in response to trauma. Oligodendrocytes (OL) and their precursor cell, OPC, also release IL-1β. Mason et al. stated that IL-1β promotes remyelination and repair using the cuprizone demyelinating model.[29]

Oligodendrocytes in the central nervous system respond to injury conditions that cause loss of axonal communication and inflammation by undergoing apoptosis. In contrast, Schwann cells in the peripheral nervous system respond by entering the cell cycle. The ability of oligodendrocytes to remove myelin debris in central nervous injury is lower or tends to be lacking when compared to Schwann cells in injured peripheral nerves. This condition explains why Wallerian degeneration in the central nervous system is very slow compared to the peripheral nerves. The presence of myelin debris in the central nervous system for a long time will inhibit axon regeneration. The immune response also affects the time for clearance of myelin debris between the central and peripheral nervous systems. The Rotshenker laboratory has found a strong correlation between the rate and timing of cytokine development and the initiation and progression of WD. They found IL-1ß and TNF levels decreased in mice with abnormally slow WD.[30] Table 3 summarizes the effects of cytokines on glial cells, endothelial cells, and endothelial cells, leukocytes, and neurons in the pathogenesis of nerve injury.

THE ROLE of SCHWANN CELLS in INJURY RESPONSE

Schwann cells are the first active component after nerve damage. Schwann cells have the potential for proliferation, modulation of immune responses, induction of neurotrophic factors, and induction of myelin axon migration, making them ideal cell components in nerve repair.[31]

Degeneration of axons at the distal nerve endings begins about two days post-injury. Schwann cells will undergo a phenotypic shift within a few hours after injury.[19,32] The presence of Schwann cell phenotypic shift helps in the regeneration of peripheral nerves. Schwann cells will differentiate into the unmyelinated and immature stages (Figure 4). This differentiation stage is characterized by upregulation of L1, NCAM, p75NTR, and glial fibrillary acid protein (GFAP). Myelin-associated genes such as myelin transcription factor Egr2, organizational and mechanical support proteins such as protein 0 (P0), myelin base protein (MBP), and myelin-associated glycoproteins are

downregulated.[33,34] In addition, this stage is also involved in the regulation and secretion of beneficial trophic factors, such as nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), ciliary neurotrophic factor (CNTF), basic fibroblast growth factor (bFGF), growth factor vascular endothelium (VEGF), and growth factor pleiotrophin.[35] The expression of macrophage-associated cytokines upregulated at this stage includes tumor necrosis factor alpha (TNF-α), LIF, interleukin (IL)-1α, IL-1β and monocyte chemoattractant protein-1 (MCP-1). Schwann cells then trigger an intrinsic myelin breakdown mechanism through autophagy, which occurs around day five after injury.[36] Myelin degeneration has an essential role in the post-injury recovery process. The presence of myelin will secrete glycoproteins associated with myelin which inhibit the axon regeneration process.[37] Schwann cells respond to nerve injury by creating a regeneration pathway, the Büngner band. The creation of Büngner bands involves the expression of many adhesion molecules, such as N-cadherin, L1, N-CAM, and extracellular matrix (ECM) molecules such as lamin fibronectin. Expression of

Table 3. Effects of cytokines in the pathogenesis of nerve damage on glia, endothelial cells, leukocytes and neurons.[28]

Cytokines	Cells	Cytokine-mediated effects
IL-1α	Oligodendrocytes	↑Remyelination; ↑differentiation of OPCs into OLs
and/or	Neurons	↑Cell death;
IL-1β	Endothelial cells	↑Endothelial-cell adhesion molecule expression; ↑chemokine production; ↓vascular stability;
	Immune cells	↑Cytokine/chemokine production; ↑innate immune cell recruitment ↑Macrophage activation ↑Astrocyte activation
	Glial	↑Microglia activation
IL-18	Immune cells	Regulates T-cell differentiation (Th1 cells with IL-12; Th2 cells with IL-4)
	Glia	↑Astrocyte/microglia activation and interaction
TNF	Oligodendrocytes	↑Apoptosis/demyelination
	Neurons	↑Apoptosis Promotes neuroprotection in the chronic phase
	Endothelial cells	↑Endothelial-cell adhesion molecule expression; ↑BBB disruption ↑Recruitment of innate immune cells
	Immune cells	↑Microglia activation
	Glia	
Fas	Oligodendrocytes	↑Apoptosis
	Neurons	↑Apoptosis; ↑axonal degeneration
	Glia	↑Apoptosis
TGF-β	Immune cells	↓Macrophage /microglia activation
	Glia	↑Astroglial scar formation; ↑fibrosis
IL-6	Oligodendrocytes	↑OL differentiation; ↑myelin production
	Neurons	↑Neurogenesis; ↑intrinsic growth capacity of sensory DRG neurpns
	Endothelial cells	↑Endothelial-cell adhesion molecule expression; influences BBB maintenance
	Immune cells	↑TNF and Il-1β expression levels; ↑innate immune cell recruitment Mediates polarization of M1 macrophages ↑Astrocyte differentiation from neural stem cells
	Glia	↑Astrogliosis
IL-10	Neurons	↑Neuronal survival
	Immune cells	↓Proinflammatory cytokine production

Table 4. Key factors controlled following damage to the peripheral nerve

No	Processes	Key factors
1	Factors involved in remyelination post-injury	NF-kB, Zeb2, HDAC1/2, Ngr1/ErbB2, Erg2/Krox20, Sox 10
2	Factors expressed during the repair program	C-Jun, Sox2, NCAM, Stat3, Robo1, p75NTR, NGF, GDNF, BDNF, TNF-a, Notch, Ngr1, HDAC1/2, VEGF-A, ERK1/2,JNK/MAPK, p38MAPK, GFAP, L1, VEGFR1
3	Factors downregulated during demyelination	Erg2/Krox20, Myelin proteins (MBP,MPZ, PMP22, Mag), Zeb2, PI3K/Akt/mTOR, Wnt, Sox10

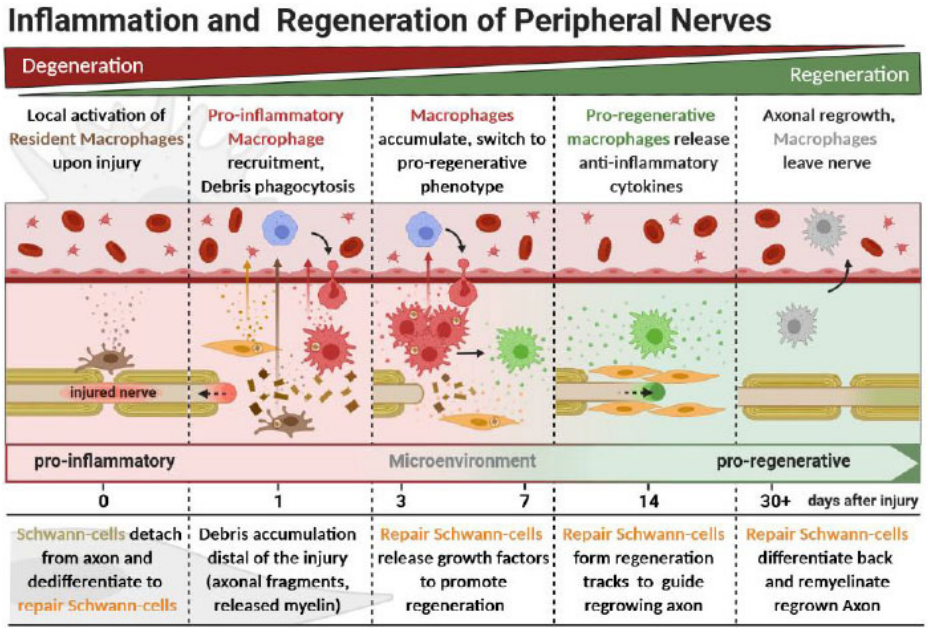

Figure 4. Peripheral nerve injury led to nerve degeneration and followed by nerve regeneration.[42]

these molecules promotes guidance and creates a microenvironment that allows the axon to regenerate and reconnect with the distal axon network properly.[38–42]

Wallerian degeneration (WD) involves an innate immune response that has an important role. The involvement of immune and non-immune cells in Wallerian degeneration plays a role in expressing cytokines and forming an effective cytokine network. Peripheral nervous system injury will express IL-1ß and other inflammatory cytokines that will trigger macrophage recruitment. The effects of these cytokines are irreversible on the initiation and control of inflammation during injury. Inflammatory cytokines expressed may also influence de-differentiation. IL-1ß causes chondrocyte de-differentiation and increases de-differentiation and proliferation of vascular smooth muscle cells. In addition, IL-1ß is also involved in the de-differentiation and proliferation of Schwann cells (Table 4).[27,28]

There are two main processes associated with Schwann cells after peripheral nerve injury: SC demyelination and SC conversion or trans-differentiation. The demyelination mechanism is characterized by the repression of pro-myelinizing genes such as Early Growth Response 2 (Erg2 or Krox20) and myelin genes such as Myelin Basic Protein (MBP), Myelin Protein Zero (MPZ or P0), Peripheral Myelin Protein 22 (PMP22) and Myelin-Associated Glycoproteins. (Mag). In addition, genes encoding L1, nerve cell adhesion molecule (NCAM), neurotrophin receptor p75 (p75NTR) and glial fibrillation acid protein (GFAP) are upregulated and re-expressed. Repair SC has differences from immature SC. The difference lies in the de-novo expression of genes such as Olig1 and Shh, and the upregulation of several proteins involved in the regeneration process. The main drivers of the SC-dependent repair program consist of (1) c-Jun is glial cell-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), neurotropin-3 (NT3), artemin, growth factor nerve endings (NGF), vascular endothelial growth factor (VEGF) and the VEGF receptor 1, which enhances the survival of injured neurons and promotes proximal axon regrowth; (2) immune response triggered by leukemia inhibitory factor (LIF), interleukin-1 alpha (IL-1α) and -1β (IL-1β), tumor necrosis factor alpha (TNF-α) and monocyte chemotactic protein 1 (MCP-1), promotes macrophage invasion and activation, blood vessel formation and myelin breakdown; (3) Changes in SC morphology and axoglial interactions including c-Jun, SRY-box 2 (Sox2) and neuregulin 1 (NRG1) in neural bridge development in the case of nerve transection and regeneration pathways through which axons regenerate; (4) Zinc finger E-box-binding homeobox 2 (Zeb2), nuclear factor-kappa B (NF-kB) and histone deacetylases 1 and 2 (HDAC1/2) are involved in the regeneration of remyelinated axons.[13,14,40]

The regenerative process requires the generation of a favorable environment and encourages axonal repair to be successful. The SC together with macrophages facilitate disintegration of distally cut axons and their rapid clearance after injury. Regeneration of axon branches is inhibited by the presence of persistent axon fragments thereby delaying axon regrowth. The SC forms a constricted actomyosin sphere along a non-fragmented distal cut axon after peripheral nerve injury. This mechanism is triggered by a distal cut of the axon with local translation induced by injury. There is upregulation of VEGFR1 agonists, PlGF, and results in activation of the VEGFR1/Pak1/F-actin axis in SCs. Myelin breaks down into small intracellular and extracellular fragments and debris at the axon site of distal injury. Myelin debris acts as a barrier to axon regeneration by creating a non-permissive environment. PNS myelin is less inhibitory than CNS myelin after nerve damage.[23,43,44]

The SC digests intrinsic myelin via macro-selective autophagy called myelinophagy in the first step after nerve damage. During this process, double membrane phagophores sequester intracellular myelin debris, which mature into autophagosomes and eventually fuse with lysosomes causing the autophagy load to be degraded. During the early stages after injury, myelinophages appear to be necessary because genetic and/or pharmacological inhibition of autophagy inhibits the breakdown of myelin proteins and lipids in injured nerves. SC and macrophages collaborate to clear extrinsic myelin during the second step after injury. SC works in the receptor-mediated phagocytosis process, namely Axl and Mertk. Both receptors belong to the TAM family of phagocytic receptors. Research has shown that there is impaired

myelin degradation in SC that lacks both receptors. SC helps in the recruitment of macrophages to the injured site. During peripheral nerve injury, macrophages play an essential role. In addition to contributing to myelin clearance, they are active in the inflammatory response, facilitating the removal of axon debris and controlling the microenvironment of the injured site, allowing efficient regeneration. SC repair expresses growth factors and chemoattractant cytokines, including MCP-1, GDNF, interleukin-6 (IL-6) and LIF during the period of peak myelin clearance after injury. These factors facilitate the recruitment and induction of pro- and anti-inflammatory macrophages (M1 and M2 macrophages).[23,43,44]

Overall, Schwann cells develop into a pro-regenerative phenotype capable of facilitating neural repair when myelin-Schwann cell transfer occurs. The SC development process is transformed by C-Jun, a single protein in post-injury distal nerve endings.[40,45]

CONCLUSION

The intricate anatomy and physiology of the PNS make it very difficult and exceedingly difficult to heal nerve damage. Complete recovery is difficult due to the loss of native signs, development of scar tissue, lack of proper vascularization, and inflammation. When attempting to restore full functioning, the different procedures used for nerve restoration, such as coaptation suturing, grafts, and conduits, pose some limitations. The growth of new NGCs, therefore, needs a clever combination of the following strategies: (i) the creation of new polymers or a mixture of polymers to better integrate with native neural tissues; (ii) the incorporation of topographical structures to improve the alignment and growth of neurites; and (iii) biological signs, such as growth factors or cellular components.

Suppose the scientific community advances the basic knowledge of the biological processes behind nerve damage and recovery. In that case, engineers can incorporate the knowledge into more complex structures to better replicate the regeneration of natural nerves and the precision of patients in terms of anatomy and biology requirements.

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Conflict of Interest

All authors stated no conflict of interest regarding this review.

Author Contribution

All authors contributed in designing and concepting the review and preparing this manuscript to publish.

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