NEURAL REGENERATION RESEARCH
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Review

# Role of transforming growth factor-β in peripheral nerve regeneration

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https://doi.org/10.4103/1673-5374.377588

Date of submission: January 16, 2023

Date of decision: March 29, 2023

Date of acceptance: April 27, 2023

Date of web publication: May 31, 2023

## Abstract

Injuries caused by trauma and neurodegenerative diseases can damage the peripheral nervous system and cause functional deficits. Unlike in the central nervous system, damaged axons in peripheral nerves can be induced to regenerate in response to intrinsic cues after reprogramming or in a growth-promoting microenvironment created by Schwann cells. However, axon regeneration and repair do not automatically result in the restoration of function, which is the ultimate therapeutic goal but also a major clinical challenge. Transforming growth factor (TGF) is a multifunctional cytokine that regulates various biological processes including tissue repair, embryo development, and cell growth and differentiation. There is accumulating evidence that TGF-β family proteins participate in peripheral nerve repair through various factors and signaling pathways by regulating the growth and transformation of Schwann cells; recruiting specific immune cells; controlling the permeability of the blood-nerve barrier, thereby stimulating axon growth; and inhibiting remyelination of regenerated axons. TGF-β has been applied to the treatment of peripheral nerve injury in animal models. In this context, we review the functions of TGF-β in peripheral nerve regeneration and potential clinical applications.

**Key Words:** myelination; nerve repair and regeneration; neurite; neuroinflammation; peripheral nerve injury; Schwann cell; transforming growth factor-β; Wallerian degeneration

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## Introduction

The peripheral nervous system (PNS) encompasses all nerves outside of the central nervous system (CNS) including cranial and spinal nerves arising from the brain and spinal cord, respectively. The PNS transfers nerve impulses to/from the CNS control limb/visceral movements or receive sensory information from the periphery including the limbs (Meder et al., 2021). Peripheral nerve injury (PNI) leads to a loss of tissue function and nerve atrophy and degeneration (Bazarek et al., 2022). Acute or chronic neuropathy results in impairment or permanent loss of motor, sensory, and autonomic functions (Clements et al., 2017), with some patients developing intractable nerve pain or paralysis (Rauschecker et al., 2020; Rahmi et al., 2022). Technological advances have led to remarkable achievements in nerve regeneration; however, existing treatments such as autologous nerve transplantation (Baradaran et al., 2021), corticosteroid drugs, and nonsteroidal anti-inflammatory analgesics (Panagopoulos et al., 2017) have drawbacks (Bassilios Habre et al., 2018). Elucidating the molecular basis of axon outgrowth following PNI is critical for developing more effective approaches for peripheral nerve regeneration (PNR).

Unlike in the CNS, peripheral nerves have the capacity to regenerate (Manganas et al., 2022). Schwann cells (SCs) produce myelin that ensheathes degenerated axons (Carnevale, 2022), and macrophages are recruited to clean up cellular debris (Min et al., 2021) to establish a microenvironment conducive to axon growth. New axons will grow along the regeneration channel (Dun et al., 2019) and reinnervate target tissues (Chen et al., 2019a), and remyelination restores axons to a functional state (Lovati et al., 2018; Li et al., 2022). Key factors mediating these processes include neurotrophic factors (Li et al., 2020), extracellular matrix (ECM) components, and cell adhesion molecules (Chen et al., 2019b; Elbaz et al., 2022), all of which can potentially be exploited for the treatment of PNI.

The transforming growth factor (TGF) family of proteins includes TGF-α and TGF-β. The former is secreted by macrophages, brain cells, and epidermal cells and is involved in the development of epithelial tissue and tissue repair following injury, similar to epidermal growth factor (Nur Azlina et al., 2017). TGF-β has been widely studied in the context of tumors and autoimmune and infectious diseases (Peck et al., 2021; Luo et al., 2022; Zheng et al., 2022), and is known to create an appropriate microenvironment for nerve regeneration by regulating SCs and the inflammatory response caused by macrophages following nerve injury (Rice et al., 2019). TGF-β also protects growing axons (Bielmeier et al., 2022) and ultimately aids functional recovery (Sulaiman and Nguyen, 2016). This review discusses the current state of knowledge on the role of TGF in peripheral nerve repair, with a focus on the molecular mechanisms that can be exploited for therapeutic applications.

## Literature Search Strategy

Full-text articles in English published from January 1997 to February 2023 describing studies on the relationship between TGF-β and peripheral nerve were identified from PubMed and included in this narrative review. The search terms were "TGF-β" combined with "PNR" or "peripheral neuropathy". The search returned 2 publications. References included in these studies were screened to identify other studies that could provide relevant information. Title and abstracts were first screened, followed by keywords (e.g., "Schwann cells" and "extracellular matrix"). The limitations of the selected studies and future research directions are also summarized.

## Cellular Mechanism of Peripheral Nerve Regeneration

Peripheral nerves are bundles of myelinated and unmyelinated nerve fibers of various shapes and sizes (Yoo et al., 2021). The inner and outer parts of nerve fiber bundles are separated by connective tissue. The outer

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***Funding:*** *The work was supported by the National Natural Science Foundation of China, Nos. 31971277 and 31950410551 (both to DY).*

***How to cite this article:*** *Ding Z, Jiang M, Qian J, Gu D, Bai H, Cai M, Yao D (2024) Role of transforming growth factor-β in peripheral nerve regeneration. Neural Regen Res 19(2): 380-386.*

perineurium is composed of collagen fibers and a small number of fibroblasts and macrophages that penetrate the basal lamina and contact epithelial cells to deliver nutrients to nerve tracts (Guo et al., 2018). The inner part of nerve fiber bundles consists of several axons wrapped with the endoneurium, and forms the blood-nerve barrier (BNB) that creates a microenvironment for axon growth (Nasoohi et al., 2022).

Physical trauma from cutting or stretching and iatrogenic injuries is the most common cause of PNI (Ceballos et al., 1999). PNI can be classified according to severity as neurapraxia, axonotmesis, and neurotmesis (Seddon, 1942), although the contemporary classification includes five categories (Sunderland, 1951; Sunderland and Roche, 1958). In second-degree injury (ie, where the axon is severed but the endoneurium is intact), nerve fibers including nerve endings on the distal end of the fractured axon of damaged neurons undergo Wallerian degeneration (WD) (Waller, 1851), which is triggered by a surge of calcium ions in the injured axon approximately 24–48 hours after injury. WDis both a response to injury and prepares the site of injury for nerve regeneration (Arora et al., 2021).

**SCs contribute to the construction of an axon regeneration channel and microenvironment**

WD is a complex process involving nerve degeneration and disintegration and clearing of debris from distal (including nerve endings) and proximal (local) axons and myelin (Li et al., 2021). Immunohistochemical analyses have shown that a variety of active substances and cellular components are involved in WD (Gomez-Sanchez et al., 2022). After degeneration, SCs wrapped around the lateral side of axons undergo dedifferentiation and cooperate with macrophages to engulf and digest disintegrated myelin debris. Meanwhile, SCs proliferate while aligning within basal lamina tubes to form Büngner bands as an axon regeneration channel that guides the trajectory of regenerating axons (Monje, 2020). Proliferating SCs express neurotrophic and cell adhesion factors and ECM proteins, and induce the upregulation of genes related to axon growth and neuron survival to provide a microenvironment that is favorable for nerve repair (Pellegatta and Taveggia, 2019; Fuertes-Alvarez and Izeta, 2021). SCs can also move a short distance to the site of injury to form a cell bridge that connects nerves at both ends and guides axon extension (Fazal et al., 2017).

**Extension and reinnervation of sprouting axons**

During WD in the distal nerve, the cell body of recovering neurons continuously delivers proteins and other nutrients to the site of injury that stimulate axon outgrowth and extension along the endoneurotic canal until synapses are formed with target cells, a process known as terminal regeneration (Yang et al., 2022). The growth rate of elongating axons ranges from 0.5 to 9 mm/day. The growth cone at the leading edge of these axons (Cammarata et al., 2016) and timely activation of SCs are key factors controlling axon outgrowth (Gonçalves et al., 2019). In a rat model of sciatic nerve injury, inhibiting the expression of genes or proteins related to SC migration resulted in misdirected axons, which slowed distal nerve repair (Li et al., 2018; Xia et al., 2020). Additionally, injury to the nerve trunk prevented distal nerve recovery due to a lack of nutritional support from SCs (Zhang et al., 2021a). The number of regenerated axons in distal nerve terminals was increased in the presence of TGF-β combined with forskolin (Sulaiman et al., 2018). These findings suggest that timely activation of SCs is an important prerequisite for axon extension and reinnervation of target tissues.

**Remyelination of regenerated axons**

Of the axons extending through regeneration channels, only the thickest contacts the target cell, after which it continues to increase in diameter and develops into a mature myelinated fiber. Remyelination is critical for the functional recovery of nerve fibers and requires various neurotrophic factors and related molecules, many of which are supplied by SCs (Sulaiman and Dreesen, 2014). SCs also insulate myelinated nerves from the surrounding environment to accelerate axon growth and maturation. The mitochondrial protein prohibitin can induce the stress response in SCs and aggravate demyelinating lesions in peripheral nerves (Park et al., 2020; Della-Flora Nunes et al., 2021). In summary, WD involves changes in neurotrophic factors and associated signaling pathways in SCs and neurons. Additional studies are needed to elucidate the molecular mechanisms underlying these changes, which can provide a basis for the development of treatment strategies for PNI.

## Transforming Growth Factor-β Function and Activation

Three TGF-β isoforms—namely, TGF-β1, TGF-β2, and TGF-β3, which share a high degree of sequence homology (> 70%)—have been identified in humans (Luo et al., 2019, 2021a). TGF-β is abundant in tissues with actively differentiating cells such as platelets in bone marrow or bone tissue (Diniz et al., 2019).

**TGF-β activation**

TGF-β is known to regulate various cellular processes but the detailed mechanisms of its activation are not fully understood. Known activators of TGF-β include integrins, proteases, and reactive oxygen species. Dysregulation of these activators leads to hyperactivation of TGF-β signaling, which has been linked to adverse effects such as tumorigenesis, inflammation, fibrosis, and immune deficiency (Maldonado and Hagood, 2021).

Before their activation, the three isoforms of TGF-β exist as large precursor proteins (pre-pro-TGF-βs) containing a conserved N-terminal signal peptide, intermediate latency-associated peptide (LAP), and C-terminal mature TGF-β peptide (Li et al., 2017). After removal of the signal peptide in the endoplasmic reticulum, two monomers of the TGF-β precursor interact with each other via the LAP to form pro-TGF-β, which is then cleaved by the protease furin in the Golgi apparatus. The cleaved pro-TGF-β is known as small latent complex; the LAP dimer of this complex undergoes conformational changes that break the noncovalent bond between LAP and mature TGF-β dimers. The small latent complex binds to latent TGF-β–binding protein, forming the large latent complex (Lockhart-Cairns et al., 2022).

Many external factors influence the production of mature TGF-β such as integrin αv, the cellular microenvironment, proteolytic enzymes, and reactive oxygen species (Keski-Oja et al., 2004; Ning et al., 2022). Environmental conditions such as temperature and pH also affect the covalent bond between LAP and TGF-β and can thus be manipulated under experimental conditions to activate TGF-β. Low-dose X-ray irradiation of the LAP–TGF-β1 complex has been found to induce the dissociation of TGF-β1 from LAP, thereby resulting in TGF-β1 activation (Stachowski et al., 2019). Matrix metalloproteinases (MMPs) are a family of zinc-containing endopeptidases involved in tissue remodeling and ECM regulation; it has been reported that some MMPs such as MMP-9 and MMP-2 regulate TGF-β activation (Muscella et al., 2020), which is also induced by the binding of LAP to integrin αvβ6 in epithelial cells and to integrin αvβ8 in endothelial cells (Ciregia et al., 2021).

**TGF-β signaling pathway**

TGF-β receptors (RI, RII, and RIII) are expressed on the surface of nearly all cells (Jann et al., 2020). Type I and II receptors (RI and RII) are serine/threonine kinases; RII binds to the mature TGF-β dimer to activate downstream signaling, whereas RI regulates the related bone morphogenetic protein (BMP) pathway as well as Mullerian inhibitor substance (**Figure 1**).

TGF-β signaling is tightly regulated at the ligand, receptor, Smad signaling, and nuclear transcription levels (Batlle and Massagué, 2019) through various mechanisms such as protein-protein interaction, post-translational modification, protein transport and degradation, intracellular localization, and Smad-DNA binding (Moustakas et al., 2002). The hallmark of TGF-β signaling is assembly of the Smad complex composed of Smad, Smad4, and phosphorylated receptor-mediated Smads (Shi et al., 2022). Smads are a group of intracellular signaling proteins and transcription factors related to the TGF-β family that comprise globular N-terminal MH1, MH2, and C-terminal domains connected by a linker (Liu et al., 2022). There are 8 Smad proteins in mammals. Smad2/3 is activated and recruited by the RI anaplastic lymphoma kinase 4/5/7 (ALK4/5/7), whereas Smad1/5/8 is phosphorylated by BMP subfamily members; both are receptor-regulated Smads (R-Smad) (Sun et al., 2022). Activated R-Smads can bind to Smad4—which is not a receptor—to form a heterotrimeric transcription complex (Derynck and Budi, 2019). Smad6 and Smad7 are inhibitors of this signaling pathway. Smad7 regulates TGF-β receptor degradation by recruiting Smad ubiquitination regulatory factor 1/2 (SMURF1/2) ubiquitin ligase to inhibit Smad signaling in a negative feedback loop, which is also important for the inhibition of tissue fibrosis (Klumpe et al., 2022).

In Smad signaling, RII first phosphorylates the intracellular GS domain of RI to activate its kinase activity; RI then phosphorylates a serine residue in the C-terminal SXS motif of R-Smad to induce the formation of the Smad complex, which is translocated to the nucleus and binds to DNA (Fu et al., 2022). The MH1 domains of R-Smad and Smad4 bind to DNA, whereas the MH2 domain binds to general transcription factors, other Smads, or chromatin readers to coregulate target gene transcription (Batlle and Massagué, 2019). The TGF-β/Smad pathway is highly conserved in terms of structure and function and has been widely studied in many organisms.

In addition to the above-described SMAD-regulated signaling pathways, TGF-β family cytokines activate other signaling molecules such as mitogen-activated protein kinase (MAPK) family members in a cell type-dependent manner, along with GTP-bound Ras protein-activated MAPK kinases (MEKs) and MAPK kinase kinases (MKKs) (Wang et al., 2019). Activated extracellular signal-regulated kinase (ERK), a MAPK, regulates downstream transcription factors such as the zinc finger protein Snail, a transcriptional repressor of E-cadherin, to modulate target gene expression. Dysregulation of TGF-β signaling is associated with autoimmunity, inflammation, and cancer (Liu et al., 2017).

**Characteristics and functions of TGF-β**

Besides TGF-β, the TGF-β superfamily includes inhibin, activin, Mullerian inhibitor substance, BMP, and growth differentiation factor (GDF), each with a distinct structure and function (Soelch et al., 2021) and functioning as a regulator of connective tissue healing, bone diseases, tumorigenesis, and tissue and organ growth and development (Chauvin et al., 2021; Lai et al., 2022). Most TGF-β family members have been implicated in PNR. GDF-15 was shown to promote axon regeneration in crushed sciatic nerve (Wang et al., 2015); activin A showed an anti-apoptotic function and protected neurons after oxygen-glucose deprivation (Xu et al., 2013); and BMP-7 expression was upregulated in dedifferentiated SCs following PNI, with SC viability increased by BMP-7 administration (Kokubu et al., 2018).

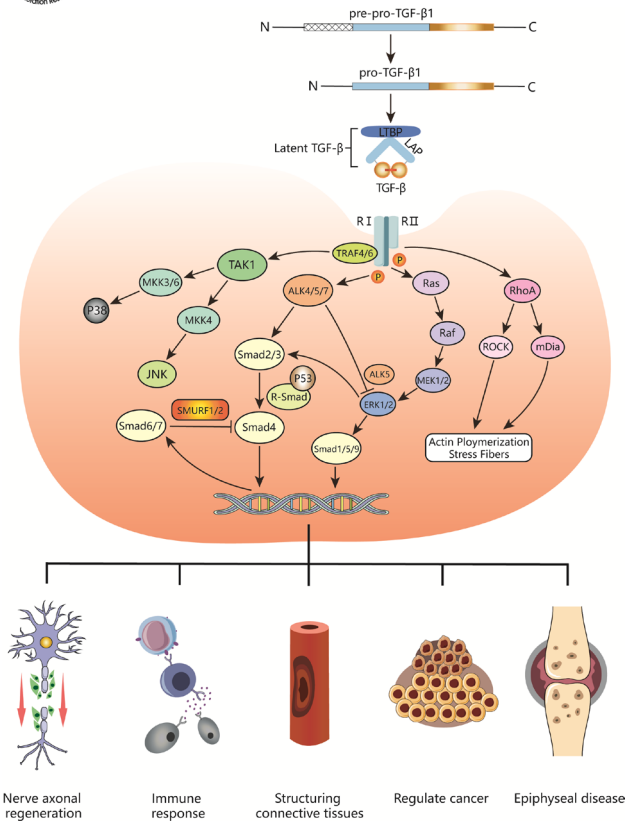


**Figure 1** | **Schematic diagram of the TGF-β signaling pathway and its regulatory effects in various tissues.**
The cleaved TGF-β precursor protein binds to LAP to form a complex; mature TGF-β is released and binds to type II receptors, phosphorylating type II and I receptors to activate the downstream Smad signaling pathway. Extracellular signal-related kinase (ERK), Jun N-terminal kinase (JNK), p38, and GTP-bound Ras proteins activate MEKs. Through these pathways, TGF-β regulates nerve regeneration, the immune response, tissue repair, and tumor growth, and bone diseases. Created using Adobe Illustrator 2022. ALK: Anaplastic lymphoma kinase; LAP: latency-associated peptide; LTBP: latent TGF-β-binding protein; mDia: mammalian diaphanousrelated protein; MEK: mitogen-activated protein; MKK4: mitogen-activated protein kinase kinase 4; Raf: rapidly accelerated fibrosarcoma; Ras: rat sarcoma; RhoA: Ras homolog family member A; RI: serine/threonine kinase-type receptors type I; RII: serine/threonine kinase-type receptors type II; ROCK: Rho-associated kinase; Smad: drosophila mothers against decapentaplegic; SMURF: SMAD specific E3 ubiquitin protein ligase; TAK1: TGF-β-activated kinase 1; TGF-β: transforming growth factor-β; TRAF4/6: tumor necrosis factor receptor-associated factor 4/6.

The functions of TGF-β overlap with those of other family members and include the regulation of both inflammation and tissue repair. TGF-β is also essential for stem cell differentiation as well as immune cell differentiation and regulation (Brûlé et al., 2021); the proliferation, differentiation, and migration of numerous cell types (Kapoor and Chinnathambi, 2023); ECM construction and remodeling (Preininger et al., 2023); and epithelial-mesenchymal transition (Jin et al., 2022). Dysregulation of TGF-β signaling is linked to the development of autoimmune, cardiovascular, and neurodegenerative diseases and cancer (Wallace et al., 2018; Hiew et al., 2021; Cheng et al., 2023). There is also accumulating evidence that TGF-β is involved in PNS-related disorders (Wang et al., 2022). Following nerve injury, macrophages, fibroblasts (Galieva et al., 2017; Nguyen and Sulaiman, 2019), SCs (Saez et al., 2019), and damaged nerves secrete TGF-β at nerve bridges to promote wound healing. Expression of the three TGF-β isoforms was detected in the distal nerve in a neonatal rat model of sciatic nerve transection, with alterations in TGF-β1 and TGF-β3 levels following injury. Notably, TGF-β1 expression first increased before decreasing during sciatic nerve regeneration (Arthur-Farraj et al., 2017). A later study found that TGF-β affected not only nerve development and regeneration, but also neuroinflammation and apoptosis after injury (Liang et al., 2022). TGF-β1 protects and promotes the repair of damaged nerves by regulating glial cell activation and proinflammatory cytokine expression. Thus, TGF-β1 may play a critical role and is a potential therapeutic target in neurodegenerative diseases (Zhou et al., 2019).

## Role of Transforming Growth Factor-β in Peripheral Nerve Regeneration

### TGF-β regulates SC viability

SCs are unique glial cells that not only remodel the myelin sheath but also provide support for unmyelinated nerve fibers. A large number of SCs are recruited to the site of PNI. After dedifferentiation into progenitor cells, SCs engulf cellular debris while secreting factors that guide axon growth and effectuate nerve repair (Fogli et al., 2019; Su et al., 2022). TGF-β is an important activator of SCs; post-injury regulation of SCs is a complex process that is influenced by injury-induced secretion of chemokines and helper molecules at the site of injury (McMorrow et al., 2022). One study that used an antibody array combined with bioinformatics analysis of protein expression at the nerve stump in a sciatic nerve injury model found that TGF-β1 expression changed significantly during WD (Gong et al., 2019). Other studies have also shown that TGF-β modulates the growth and differentiation, proliferation, apoptosis, and migration of SCs (Wang et al., 2013; Gong et al., 2022).

Following PNI, timely activation of SCs at the site of injury is essential for PNR. Co-application of TGF1-β1 and forskolin following chronic denervation and axon transection was shown to promote mitosis, with activated SCs stimulating axon regeneration (Huang et al., 2017). Additionally, fibroblast growth factor-7 (FGF7), myelin basic protein (MBP), and peripheral myelin protein 22 (PMP22) expression levels were markedly increased in SCs cultured in the presence of TGF-β1 inhibitor (Nguyen and Sulaiman, 2019).

TGF-β1 regulates the proliferation and apoptosis of SCs in damaged nerves, thereby controlling SC population size (Cristobal and Lee, 2022; Ge et al., 2022). Exogenous TGF-β1 exhibited pro-proliferative effects in adult rat primary SC cultures (Li et al., 2015). However, in an *in vitro* study, tumor necrosis factor-α (TNF-α) and TGF-β1 acted synergistically to induce SC death. Thus, environmental factors limit the regulatory effects of TGF-β on SC proliferation and apoptosis (Luo et al., 2021b).

TGF-β cooperates with SCs to promote axon growth (Mo et al., 2012). SCs at the site of nerve injury function as a "bridge" to guide the extension and joining of severed nerve endings. This process requires the participation of various cofactors. MMPs degrade and remodel the ECM (Mo et al., 2012). However, it was recently demonstrated that *MMP9* knockdown and overexpression in cultured rat SCs inhibited and promoted cell migration, respectively (Lu et al., 2022). Another study found that MMPs bind to CD44 to release TGF-β1, reducing inflammation at the site of injury and stimulating the release of vascular endothelial growth factor to promote angiogenesis and neural bridge formation by SCs (Cattin et al., 2015; Hsu and Hsieh, 2022). Thus, inhibiting TGF-β1 release can inhibit angiogenic signals, interfere with neovascularization and SC guidance activity, and ultimately impact the repair of damaged nerves (Huang et al., 2023).

Fibrosis is the main cause of irreversible nerve damage. As a major profibrotic cytokine, TGF-β1 has therapeutic potential for preventing fibrosis through regulation of SC phenotype reprogramming, which can lead to transdifferentiation, connective tissue cell expansion, and fibrogenesis in damaged peripheral nerves. Fibronectin expression was shown to be upregulated in SCs stimulated by TGF-β1, an effect that was abrogated by the TGF-β1 type I receptor (ALK5) inhibitor SB-431542 (Petito et al., 2013).

### TGF-β regulates inflammation following nerve injury

PNR depends on the healing capacity of injured axons and involves coordination between various non-neuronal cell types. SCs recruit macrophages to the site of injury to clear myelin debris but also trigger local inflammation, which can hinder peripheral nerve repair (Yadav et al., 2022). In a rat model of sciatic transection, electrophysiologic and behavioral analyses showed that depletion of inflammatory factors was beneficial for the recovery of neurologic function (Chen et al., 2021).

In the nervous system, TGF-β exerts anti-inflammatory effects through the regulation of lymphocyte activities. Embryonic mice with mutations in alleles of *TGF-β* in stem cells died of a mixed inflammatory cell response and tissue necrosis after birth (Choi et al., 2022). In mammals, most innate immune cells including B cells, T cells, dendritic cells (DCs), and macrophages secrete TGF-β, which modulates the proliferation, differentiation, and activation of immune cells through negative regulation of cytokines (Yamamoto-Furusho and Parra-Holguín, 2021; Czaja, 2022).

Macrophages are the most prominent immune cell type involved in PNI and repair and can be categorized as classically and selectively activated macrophages (M1 and M2, respectively) (Liu et al., 2019). Following PNI, SCs release macrophage migration inhibitory factor to recruit macrophages to the site of injury, which not only contributes to WD but also induces the polarization of macrophages into the anti-inflammatory M2 phenotype to promote axon regeneration (Yin et al., 2022). Under the action of IL-4 and IL-13, M2 macrophages are induced to differentiate into M2a, M2b, and M2c subtypes. M2a releases anti-inflammatory factors including TGF-β to promote cell activity and reduce inflammation (Shen et al., 2021). Macrophage-secreted TGF-β was shown to enhance the expression of some neurotrophic factors (Stewart et al., 2020), whereas M2c macrophages at the site of injury were activated by TGF-β and other anti-inflammatory factors to accelerate the resolution of the inflammatory response, thereby aiding tissue repair and stimulating ECM synthesis (Liu et al., 2019). M2 macrophages can also be induced to differentiate into M1 macrophages by specific external stimuli such as increased levels of the lactoferrin immune complex, and M2b and M2d subtypes of M1 macrophages have the capacity to enhance wound recovery and angiogenesis (Wyatt-Johnson and Brutkiewicz, 2020; Chen et al., 2022).

**Table 1** | **The roles of TGF-β pathways in promoting peripheral nerve regeneration**

| Cells | functions | Activation pathway | Acting factors | References |
|---|---|---|---|---|
| SCs | Promote cell migration/invasion | Smad2 | MMP-2 | Muscella et al., 2020 |
| | | ERK1/2, JNK1/2, NF-κB | MMP-9 | |
| | | Eph | N-cadherin | Clements et al., 2017 |
| | Inhibit cAMP-dependent myelin protein expression and myelination | cAMP pathway | myelin protein | Jessen and Mirsky, 2022 |
| | Promote reprogramming | c-Jun | NCAM and L1 | |
| | Recuperate migration | external stimulation via TGF-β | ErbB3 | Hortells et al., 2021 |
| M2 macrophage | Anti-inflammation | M2a selective activation | TGF-β | Liu et al., 2019 |
| Tregs | Drive pathogenic Th17 cell differentiation | ALK4-ERK | Activin-A | Wu et al., 2021 |
| Perineurial glia | Drive perineurial glial bridging | Smad3 | CTGFa | Arena et al., 2022 |
| Peripheral nerve pericytes | Regulate the capillary structure and thickness of the basal lamina | Release TGF-β by peripheral nerve pericytes | lamina-related protein | Lange et al., 2016 |

ALK4: Anaplastic lymphoma kinase; cAMP: cyclic adenosine monophosphate; CTGFa: connective tissue growth factor-a; Eph: erythropoietin-producing human hepatocellular receptors; ErbB3: erb-b2 receptor tyrosine kinase 3; ERK: extracellular regulated kinase; JNK: c-Jun N-terminal kinase; L1: L1 cell-adhesion molecule; MMP-2: matrix metalloproteinases-2; NCAM: neural cell adhesion molecule; NF-κB: nuclear factor-kappa B; SCs: Schwann cells; Smad: small mother against decapentaplegic; TGF-β: transforming growth factor-β; Treg: regulatory T cell.

$CD4^+$ and $CD8^+$T lymphocytes were shown to migrate to the site of injury in response to TGF-β (Zhang et al., 2021b; Dong and Ubogu, 2022). TGF-β1 inhibits the function of regulatory T cells (Treg) and antigen-presenting DCs and maintains Treg cell numbers (Ryu et al., 2012). In the inflammatory response, $CD4^+$ T cells are induced to differentiate into effector T cells such as Th1, Th2, Th17, and Treg by antigen-presenting cells. Th17 is a helper T cell that is induced to differentiate from Th0 cells by IL-6 and IL-23. This cell type is regulated by TGF-β (Zöller et al., 2018). In a mouse model of autoimmune neuroinflammation, expression of the TGF-β superfamily cytokine activin-A was upregulated, which along with IL-6, induced pathogenic Th17 differentiation (Morianos et al., 2020). However, knockdown of activin-A and its receptor ALK4 *in vitro* and *in vivo* suppressed Th17 cell differentiation. ERK phosphorylation is a prerequisite for the differentiation of pathogenic Th17 cells, and phosphorylated ERK is inhibited by TGF-β1/ALK5 but not by activin-A/ALK4. Th17 cells and activin-A/ALK4/ERK are thought to regulate neuroinflammation *in vivo* (Wu et al., 2021). Thus, the existing evidence indicates that TGF-β regulates neuroinflammation in PNI.

### TGF-β promotes the construction of regeneration channels

The ECM is a network of proteins synthesized and secreted by animal cells including laminin, fibronectin, type IV and V collagen, and heparin sulfate proteoglycan (Graham et al., 2019). These factors are mainly located in the basal lamina of SCs wrapping nerve fibers and are produced by SCs (Gonzalez-Perez et al., 2018). After PNI, the expression of matrix proteins—mainly laminin—increases rapidly, and these proteins cooperate with SCs to guide axons into basal lamina tubes and establish scaffolds with Büngner bands (Mikdache et al., 2022).

Fibronectin is a matrix proteins that is thought to promote cell fibrosis and tissue repair by interacting with growth factors including BMPs of the TGF-β superfamily and unactivated latent TGF-β-binding proteins (Chute et al., 2019). TGF-β regulates ECM to control the differentiation and migration of SCs, thereby promoting nerve repair. During WD, TGF-β was observed to be secreted both in the distal and proximal ends of the injury site (Luthold et al., 2022), promoting the invasion of SCs through N-cadherin and acting coordinately with ephrin signaling to induce the migration of SCs at the injury site (Clements et al., 2017). ErbB3 is an SC receptor for the neuronal ligand neuregulin-1; ErbB3 knockdown in mice with PNI delayed SC migration and reduced myelin thickness (Gibson et al., 2018; Hassan et al., 2022). A comparative analysis of gene expression in cultured dorsal root ganglia from ErbB3-deficient and wild-type mice showed that periostin expression was downregulated in the former, which was associated with reduced migration of SCs; these effects were abrogated by application of exogenous TGF-β (Hortells et al., 2021; Ben Amar et al., 2022).

### TGF-β and BNB

The BNB is an interface for material exchange between the endoneurial capillary wall and extracellular space. It is composed of tightly connected endothelial cells and is selectively permeable to proteins, ions, and hormones in the surrounding environment (Grüter et al., 2020). In WD, the BND disintegrates and then reassembles along the degenerated axon to protect and stabilize the microenvironment during nerve repair (Ubogu, 2020).

Glia in the PNS are an important constituent of the BNB, generating nerve membranes to cover the outer layer of SCs and axons and producing factors required by the BNB to protect the nerve (Jurisch-Yaksi et al., 2020; Neely and Lyons, 2021). In zebrafish, SCs are interconnected with perineurial glia. Perturbation of SC growth was shown to slow BNB formation whereas interfering with peripheral glial cell activity disrupted the growth and differentiation of SCs (Kucenas, 2015; Reed et al., 2021). TGF-β was found to regulate downstream effectors and connective tissue growth factor-a to guide the bridging of peripheral glial cells in a positive feedback loop (Arena et al., 2022).

Peripheral nerve pericytes are another cell type closely associated with the BNB. Pericytes release basal lamina-related factors such as fibronectin, collagen IV, and tissue inhibitor of metalloproteinase-1 (TIMP-1) as well as TGF-β to modulate capillary structure and basal lamina thickness (Lange et al., 2016).

TGF-β can also regulate the permeability of other blood barriers through specific signaling pathways. In a rat model of spinal cord injury, exogenous TGF-β activated Smad2/3 to reduce inflammation and enhanced the expression of tight junction proteins, thereby reducing the permeability and restoring its function of the blood-spinal cord barrier (Nakazaki et al., 2021; Soares et al., 2022).

## Discussion

The evidence to date indicates that TGF-β family proteins are essential for cell differentiation and migration, axon regeneration and guidance, and regulation of the immune response following PNI. TGF-β contributes to wound repair by directly or indirectly regulating various cell types and factors involved in these processes (**Figure 2**).

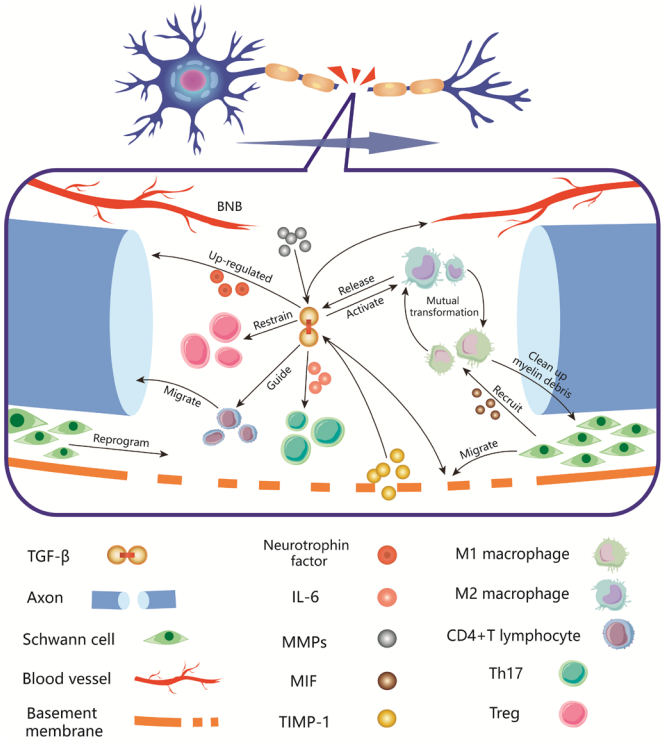


**Figure 2** | **Different roles of TGF-β in PNR.**
Following PNI, TGF-β activates SCs at the site of injury to guide axon growth. SCs recruit a large number of macrophages and TGF-β regulates their differentiation and that of other lymphocytes to control the inflammatory response. TGF-β also regulates the secretion of peripheral glial cell- and pericyte-related proteins (including fibronectin, collagen IV, and tissue inhibitor of metalloproteinase-1 [TIMP-1]), which changes the permeability of the BNB and basal lamina thickness, thereby helping to establish a microenvironment that is conducive to PNR. Created using Adobe Illustrator 2022. BNB: Blood-nerve barrier; FN: fibronectin; IL-6: interlukin-6; MIF: migration inhibitory factor; MMPs: matrix metalloproteinases; TGF-β: transforming growth factor-β; Th17: T helper cell 17; TIMP-1: tissue inhibitor of metalloproteinase-1; Treg: regulatory T cell.

With advances in medical technology, tissue engineering based on the delivery of growth factors that play an important role in tissue repair is becoming increasingly feasible. Animal experiments using biomaterial carriers have yielded promising results (Koria, 2012). The delivery of TGF-β by biopolymer gels and scaffolds in experimental models of PNI was shown to accelerate nerve repair and functional recovery (Kubiak et al., 2020; Nuelle et al., 2022). However, the structure of the biomaterial and TGF-β dosing require optimization, while charge interference between polymer materials and TGF-β, potential adverse effects, and factors affecting the delivery of TGF-β to cells are outstanding challenges that need to be overcome for clinical applications (Miwa et al., 2022). We speculate that TGF-β has dual roles (ie, stimulatory and inhibitory) in PNR, similar to those observed in tumorigenesis. In one study, injection of TGF-β into the injured rat brain promoted the formation of dense fibrous scars that prevented axon outgrowth (Ayazi et al., 2022). Whether similar effects occur in peripheral nerves remains an open question.

## Conclusion and Prospects

In the review, we described the characteristics, function, activation, and receptors of TGF-β as well as related signaling pathways, and summarized the roles of TGF-β in peripheral nerve repair and regeneration. TGF-β plays important roles in PNR including regulating cellular survival, growth, proliferation, differentiation, migration, neuroinflammation, and neurotrophic factor secretion. Consequently, TGF-β family proteins have wide-ranging biological effects, some of which await further exploration. Future studies should focus on how to exploit the growth-promoting effects of TGF-β family members in PNR and improve the clinical applications of TGF-β, which would require collaboration between researchers and clinicians in regenerative medicine, chemistry, engineering, and pathology.

**Author contributions:** *ZD, MJ and DY designed and conceptualized the manuscript. ZD, MJ, JQ, DG and DY contributed to writing the manuscript. MJ and DY edited and formatted the manuscript. MJ, MC, HB, and DY revised, supervised and corrected the manuscript. ZD, MJ, and MC created the figures and figure legends. All authors read and approved the final manuscript.*
**Conflicts of interest:** *The authors declare that there are no competing interests.*
**Data availability statement:** *Not applicable.*


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*C-Editor: Zhao M; S-Editor: Li CH; L-Editors: Li CH, Song LP; T-Editor: Jia Y*