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Molecular and cellular mechanisms underlying peripheral nerve injury-induced cellular ecological shifts: Implications for neuroregeneration

Limao Wu [a], Jinglan He [b,*], Na Shen [c], Song Chen [d]

[a] School of Clinical Medicine, Hebei University of Engineering, No.81 Congtai Road, Congtai District, Handan City, Hebei Province 056004, China
[b] Affiliated Hospital of Hebei University of Engineering, No. 80, Jianshe Street, Fuxing District, Handan City, Hebei Province 056003, China
[c] Department of Science and Education, Affiliated Hospital of Hebei University of Engineering, No.81 Congtai Road, Congtai District, Handan City, Hebei Province 056004, China
[d] Orthopaedic Center, Affiliated Hospital of Hebei University of Engineering, No.81 Congtai Road, Congtai District, Handan City, Hebei Province 56004, China

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ABSTRACT

The peripheral nervous system is a complex ecological network, and its injury triggers a series of fine-grained intercellular regulations that play a crucial role in the repair process. The peripheral nervous system is a sophisticated ecological network, and its injury initiates a cascade of intricate intercellular regulatory processes that are instrumental in the repair process. Despite the advent of sophisticated microsurgical techniques, the repair of peripheral nerve injuries frequently proves inadequate, resulting in adverse effects on patients' quality of life. Accordingly, the continued pursuit of more efficacious treatments is of paramount importance. In this paper, a review of the relevant literature from recent years was conducted to identify the key cell types involved after peripheral nerve injury. These included Schwann cells, macrophages, neutrophils, endothelial cells, and fibroblasts. The review was conducted in depth. This paper analyses the phenotypic changes of these cells after injury, the relevant factors affecting these changes, and how they coordinate with neurons and other cell types. In addition, it explores the potential mechanisms that mediate the behaviour of these cells. Understanding the interactions between these cells and their mutual regulation with neurons is of great significance for the discovery of new neuroregenerative treatments and the identification of potential therapeutic targets.

1. Introduction

Peripheral nerve injury represents a prevalent form of injury within the nervous system, typically resulting from traffic accidents, falls, or sports-related trauma. Estimates suggest that peripheral nerve injury accounts for 2–3 % of clinical trauma cases (Liu et al. 2022). Such injuries result in sensory and motor dysfunction of the limbs, significantly impairing patients' quality of life and frequently leading to the development of psychological disorders (Wojtkiewicz et al., 2015). In comparison to the central nervous system (CNS), the peripheral nervous system (PNS) demonstrates superior regenerative capacity following injury, exhibiting faster and more complete regression (Vargas and Barres, 2007); Additionally, the remarkable plasticity of peripheral nerve glial cells (Boerboom et al., 2017), enhanced adaptability to diseases and injuries, and robust regenerative and reparative capabilities (Taveggia and Feltri, 2022) contribute to this phenomenon. Despite the regenerative capacity of the peripheral nervous system being reflected in early in situ repair or autograft repair (which represents the gold standard of treatment (Rao et al., 2022)) after nerve injury, patient satisfaction with functional recovery remains low. The reasons for patient dissatisfaction are diverse and encompass a range of factors, including slow nerve regeneration, muscle fibrosis and atrophy, disrupted axonal regeneration, inadequate target organ reinnervation, and insufficient ecological regulation of the nerve fibers themselves and their surrounding cells (Allodi et al., 2012). In particular, the cellular ecosystem in peripheral nerves is highly intricate and susceptible to disruption. It encompasses a multitude of cell types, including chevron cells, immune cells, vascular-associated cells, and fibroblasts, which are intricately connected to neurons through their interactions and play a pivotal role in axonal regeneration (Fornasari et al., 2020; Ren et al., 2024). An understanding of the ecological changes that occur in these cells following nerve injury may facilitate the development of more effective treatments. Accordingly, this paper reviews the ecological changes of these peripheral cells after peripheral nerve injury (PNS), with the

* Corresponding author.
E-mail addresses: 562122050@qq.com (L. Wu), hejinglan@hebeu.edu.cn (J. He), shenna1982@hebeu.edu.cn (N. Shen), chensong@hebeu.edu.cn (S. Chen).

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objective of providing theoretical ideas and research directions for researchers.

2. The ecology of neuronal cells

Peripheral neuronal cells constitute the functional units of the Peripheral Nervous System (PNS), playing a pivotal role in transmitting commands from the Central Nervous System (CNS) to various body parts and collecting sensory information such as touch, pain, and temperature sensations. These inputs are then relayed back to the CNS for processing. At an early stage, peripheral neurons extend in a peripheral direction in order to complete the pseudo-unipolarisation process, forming a T-shaped structure. This process results in the formation of axons that are distributed to various tissues in the periphery (Meltzer et al., 2021). Neurons depend on axonal transport mechanisms for the paracrine transport of substances, including proteins, RNA, and organelles, to growth cones and synapses. These mechanisms also regulate the retrograde transport of autophagy-lysosomal degradation, neurotrophic factor signalling, and the response to nerve injury, thereby ensuring neuronal function and viability (Sleigh et al., 2019). Peripheral Neuronal Injury (PNI) can disrupt this system, resulting in axonal disruption, cellular atrophy, and even apoptosis in some neurons. However, surviving neurons can initiate a regenerative mechanism, transitioning from a transmitter to a pro-differentiation state and upregulating genes associated with regeneration (El Chemali et al., 2024). For instance, following axonal injury, an increase in neuronal nitric oxide levels induces surrounding neuroglial cells to release erythropoietin. This glycoprotein binds to neuronal receptors, preventing further degeneration of intact axons (Oliveira et al., 2023). However, adenosine 5′-monophosphate (AMP)-activated protein kinase (AMPK) was identified as a specific target for downregulation in damaged peripheral axons, indicating a potential role for AMPK in axonal regeneration (Kong et al., 2020). Furthermore, the phosphorylation of STAT3, the activation of cJun and ATF3, the CAMP and PKC signalling pathways are also closely associated with axonal regeneration following injury (De Virgiliis et al., 2020; Wu et al., 2018). Post-injury, neurons not only self-regulate but also interact with surrounding cells. Neurons can induce endothelial cells (ECs) to differentiate and form microvessels, facilitating axonal regeneration (Bates et al., 2002). Peripheral nerve glial cells provide metabolic support and nutrients to neurons, maintaining physiological activities and releasing neurotransmitters to modulate the neuronal environment (Davies, 1998); Schwann cells (SCs) contribute to the myelination, maintenance, and regeneration of neuronal axons (Della-Flora Nunes et al., 2021); These interactions ensure effective regeneration of peripheral nerves following injury. In summary, peripheral neuronal cells play a crucial role within the PNS, tasked with both transmitting CNS directives and collecting sensory information. Post-PNI, these cells face significant challenges including axonal breakage and cellular atrophy. However, surviving neurons are capable of activating regenerative mechanisms that collaborate with other cell types, including satellite glial cell, Schwann cells, and endothelial cells, to facilitate the regenerative process following injury. This cell-cell interaction is crucial for the effective regeneration of peripheral nerves and provides a significant theoretical foundation for the development of novel therapeutic strategies for nerve injury.

3. Ecology of glial cells

3.1. Classification and function of glial cells

Glial cells are the essential supportive cells within the nervous system and play a crucial role in the event of injury. In the peripheral nervous system (PNS), glial cells primarily consist of Schwann cells (SCs) and satellite glial cells (SGCs), which rapidly respond to injury both morphologically and functionally to promote neuronal survival and regeneration. Schwann cells are categorized into two types based on their myelin production: myelinated Schwann cells (MSCs) and non-myelinated Schwann cells (NMSCs). MSCs surround larger axons, forming multi-layered myelin structures, whereas NMSCs envelop smaller axons, forming Remak bundles (Jessen and Mirsky, 2016; Sango, 2023). Additionally, there is a highly specialized type of terminal Schwann cell (TSC) located at nerve endings in the PNS that supports tissue growth, development, and repair after injury. All these Schwann cells originate from neural crest cells (NCCs), which differentiate into multipotent SC precursors (SCPs) during development, then migrate and differentiate into SCs with various functions (Hastings and Valdez, 2024). The function of these SCs is mainly to form and maintain myelin sheaths, which are essential for the efficient propagation of nerve signals (Della-Flora Nunes et al., 2021), and the quality of myelin sheath formation in turn determines functional recovery after nerve regeneration (Jiang et al., 2022). Therefore, myelination plays a very important role in the process of nerve regeneration. Each SC myelinates only one segment of a single axon during myelination (Nave and Werner, 2021), enhancing the transmission speed and efficiency of nerve impulses by controlling axon protein synthesis and caliber, and coordinating the formation and maintenance of Ranvier nodes (Court et al., 2008; Elazar and Peles, 2020). After PNS injury, SCs detach from axons and undergo phenotypic changes. These changes activate cellular transcription factors, genes, and signals, leading to the release of neurotrophic factors that support the survival of damaged neurons and facilitate myelin debris removal and axon regeneration (Nocera and Jacob, 2020; Sango, 2023). SCs play a critical role in axon regeneration by providing lactate and iron, which support the metabolic needs of axons (Deck et al., 2022; Mietto et al., 2021; Taveggia and Feltri, 2022; Zilic et al., 2016). In contrast, SGCs in DRG exhibit numerous characteristics analogous to those of macrophages, including the expression of cytoplasmic proteins, membrane neurotransmitter receptors,transporters and ion channels (e.g. K^{+}), and release neuroactive substances, including adenosine triphosphate (ATP) and cytokines, as part of the signaling process between glia and neurons. Furthermore, SGCs utilize Ca^{2+} as a signaling molecule, which plays a pivotal role in regulating the functions of surrounding cells (Jager et al., 2020; Rabah et al., 2020). Following peripheral neuronal injury, SGCs increase the synthesis and activation of cyclic guanosine monophosphate (cGMP), which is associated with the development of pain (Hanani, 2022), Concurrently, there is a notable elevation in the expression of neurotrophin receptor p75NTR, glial fibrillary acidic protein (GFAP), and gap junction protein connexin-43 (Nadeau et al., 2014). It has been documented in the scientific literature that SGCs are in close proximity to resident macrophages and initiate each other's activity, while simultaneously regulating injured neurons in a synergistic manner (Krishnan et al., 2018). SGCs envelop the cell bodies of sensory neurons and participate in the regulation of the microenvironment, metabolism, signal transduction, nutritional support, debris clearance, protective barrier (Qarot et al., 2024), and ion concentration, providing important support for axon regeneration (Lima et al., 2022; Tasdemir-Yilmaz et al., 2021; Wiltbank and Kucenas, 2021). In summary, glial cells play a supportive role in the nervous system, especially after PNS injury. Schwann cells and satellite glial cells work together to promote neuronal survival and functional recovery by forming myelin sheaths, providing nutrient support, regulating the microenvironment, and promoting axonal regeneration in a variety of ways.

3.2. The signaling and mechanistic alterations that occur in SCs following PNI

Schwann cells (SCs), as crucial non-neuronal elements in the Peripheral Nervous System (PNS), envelop nerve fibers and form myelin sheaths. Injury triggers SCs to initiate inflammatory and immune response regulation, neurotrophic signaling pathway modulation, and cytoplasmic restructuring. These cells undergo a series of dedifferentiation, proliferation, phenotypic changes, and basement membrane

remodeling, which are critical for guiding axonal regeneration and repair. These transformations enable SCs to adapt to the damaged environment and play a pivotal role in the restoration of nerve function (Table 1).

3.3. The role of SCs and their products in nerve regeneration

Schwann cells (SCs) play a crucial regulatory role in nerve regeneration, not only through their direct cellular actions but also by secreting a variety of products. These include:

Epidermal Growth Factor Betacellulin (Btc): Secreted by SCs, Btc regulates neuronal behavior and increases neurite length, thereby promoting nerve regeneration (Wang et al., 2021).

Table 1
Relevant signaling mechanisms and roles affecting SCs.

Relevant signals affecting SCs	functional role
Sox10	Essential for development, differentiation, and myelin regeneration (Gokey et al., 2012)
LIF	Influences proliferation and migration, promoting peripheral nerve regeneration (Q. Chen et al., 2021)
Krox-20 and Krox-24	Mediate lineage development and differentiation (Topilko et al., 1997)
MIF	Prevents apoptosis and accelerates peripheral nerve regeneration (Nishio et al., 2002)
N-cadherin	Critical for connection, growth, and axonal alignment (Wanner and Wood, 2002)
PI4KB	Crucial for normal myelin formation (Baba et al., 2020)
lnc-RMRP	Plays an important role in proliferation and migration (Zhou et al., 2022)
miR−221/222	Associated with phenotypic regulation (Yu et al., 2012)
miR−340	Related to fibrinolytic activity, migration capability, cellular debris clearance, and axonal regeneration (Li et al., 2017)
miRNA−21	Internalized by peripheral neurons to promote axonal regeneration (López-Leal et al., 2020)
Rheb	Regulated mitochondrial pyruvate metabolism Critical for the stability of peripheral axons (Jia et al., 2021)
Mitochondria	Play a key role in axonal development and maintenance (Ino and Iino, 2017)
PKM2 and lactate	Essential for maintaining axonal physiology and function through myelination (Deck et al., 2022)
TREM2	Glycolysis and oxidative metabolism regulation Provides neuroprotective effects (Zhang et al., 2024)
BCAT1	Activation of the Twist/Foxc1andSOX2 axis. Improves nerve function and myelin regeneration (Chen et al., 2023)
Autophagy	Involved in myelin debris degradation, clearance, and formation (Li et al., 2020)
TGF-β	activation of the Smad and AKT pathways.Regulates proliferation and apoptosis (Li et al., 2015)
LKB1-AMPK and mTORC1	Controls axonal integrity and myelination (Beirowski, 2019)
NRG1/ErbB2	Enhances proliferation, migration, regeneration, myelination, and functional recovery (Newbern and Birchmeier, 2010)
Notch signaling	Effectively promotes nerve repair in the early stages of regeneration (J. Wang et al., 2015)
ERK1/2 and p38	Mediate dedifferentiation, proliferation, cell migration, and accelerate myelin formation (Wei et al., 2024)
JNK/c-Jun	Mediates myelin digestion (Gomez-Sanchez et al., 2015)
PI3K/Akt	Essential for migration, proliferation, and myelin regeneration (Dong et al., 2019)

LIF:Leukemia inhibitory factor, Krox-20 (EGR2):early growth response gene 2, Krox-24 EGR1:early growth response protein 1, MIF:macrophage migration inhibitory factor, PI4KB:phosphatidylinositol 4-kinase β, lncRMRP:long-chain non-coding RNA RMRB, Rheb:RAS homologous protein, PKM2:pyruvate kinase 2, TREM2:myeloid cell-2 triggering receptor,BCAT1: branched-chain aminotransferase 1,TGF-β: transforming growth factor-β, LKB1-AMPK:hepatic kinase B1-AMP-activated protein kinase, mTORC1:rapamycin-targeting protein complex 1,NRG-1:neuromodulin-1, ErbB(Tyrosine kinase receptor), ERk: extracellular signal-regulated kinase, JNK:c-Jun N-terminal kinase, PI3K/Akt: phosphatidylinositol-3 kinase/protein kinase B.

Neurotrophic Factors: Transported retrogradely to the neuron body, these factors support neuronal survival and provide essential nutritional support for nerve regeneration (Davies, 1998).

VEGF-Related Factors: These induce the differentiation of endothelial cell (EC) precursors and promote angiogenesis, supplying abundant blood needed for nerve regeneration (Mukouyama et al., 2002).

Semaphorin 3E (Sema3E): A synthetic protein that binds to downstream receptors to promote SC proliferation and migration, accelerating the nerve repair process (Shen et al., 2022).

Exosomes: SC-derived exosomes act through multiple mechanisms, including enhancing autophagy and reducing apoptosis via the EGFR/Akt/mTOR pathway to protect axons from damage. Additionally, they enhance the glycolytic metabolism of ECs, promoting vascular reconstruction, axonal regeneration, and functional recovery post-injury. Exosomes also protect neurons directly by blocking caspase-3 activity (Oliveira et al., 2023; Pan et al., 2022; Sun et al., 2024).

Multifunctional Glycoprotein Milk Fat Globule-EGF Factor 8 (MFG-E8): Acts through the SOCS3/STAT3 pathway to inhibit neuronal apoptosis, providing protection for neuronal survival (Ren et al., 2023; Wang et al., 2023).

Integrin-β1: Promotes proliferation, migration, and angiogenesis of endothelial cells(ECs), while reducing tissue damage, thus positively impacting nerve regeneration and tissue repair (Huang et al., 2022).

Overall, SCs exert a key influence on nerve regeneration by secreting a variety of bioactive products, including growth factors, neurotrophic factors, synthetic proteins, exosomes, and multifunctional glycoproteins. These substances promote neuronal survival, angiogenesis, axonal protection, and metabolic support through diverse mechanisms. The intricate interactions and regulatory mechanisms highlight the multifaceted role of SCs in nerve regeneration and underscore the importance of further research into these cells and their products in the context of nerve damage and repair.

3.4. Transcription factors and growth factor-related proteins mediating SCs in nerve regeneration

Transcription factors (TFs) and growth factors play pivotal roles in Schwann cell (SC)-mediated nerve regeneration. TFs orchestrate the nerve regeneration process by participating in SC differentiation, axonal selection, and myelination (Xu et al., 2023). For instance, the transcription factor B-cell lymphoma/leukemia 11A (BCL11A) regulates the activity of SCs by binding to the promoter regions of their nuclear receptors (Zhang et al., 2023). Growth factors are equally crucial for SC proliferation, migration, and axonal regeneration (Kadomatsu and Muramatsu, 2004). Following nerve injury, SCs upregulate the expression of various growth factors to promote nerve regeneration and repair. These include Brain-Derived Neurotrophic Factor (BDNF), Nerve Growth Factor (NGF), and Glial cell line-Derived Neurotrophic Factor (GDNF), which collectively support nerve regeneration. Additionally, the upregulation of Neurotrophic Factors (NTFs) aids in neuronal survival and axonal regeneration (Hu et al., 2023; Richner et al., 2014). Beyond these, other growth factors such as Ciliary Neurotrophic Factor, Fibroblast Growth Factor-2 (FGF-2), and Neurotrophin-3 (NT-3) also experience upregulation after nerve injury, enhancing the regenerative potential of peripheral neurons by binding to specific receptors (Brushart et al., 2013; Romero et al., 2007). Therefore, transcription factors and growth factors are key regulatory molecules in nerve regeneration. They promote nerve repair post-injury by controlling SC differentiation, proliferation, migration, and myelination, and by fostering neuronal survival and axonal regeneration. Particularly, the upregulated expression of molecules such as BCL11A, BDNF, NGF, GDNF, FGF-2, and NT-3 after nerve injury underscores their importance in enhancing nerve regeneration potential. Understanding the specific mechanisms of these molecules is crucial for developing new therapies to promote nerve regeneration.

4. Immune cells

Following peripheral nerve injury, immune cells rapidly converge at the site of damage, including macrophages, neutrophils, and lymphocytes. Macrophages, in particular, are among the primary immune cells that migrate early to the injury site. They play crucial roles by phagocytizing and clearing debris from damaged myelin sheaths, secreting anti-inflammatory cytokines and chemokines to recruit other immune cells, thereby mitigating the inflammatory response and promoting nerve repair.

4.1. Macrophages

4.1.1. Functions and phenotypes of macrophages

Macrophages, derived from myeloid progenitor cells, exhibit significant heterogeneity and high plasticity, adapting their phenotypic functions according to changes in the local microenvironment (Brown et al., 2012; Gordon and Taylor, 2005). They are distributed widely throughout various tissues in the body, including within the nervous system where they are located between the nerve endoneurium and myelin sheaths, closely interacting with axons. Their primary functions include phagocytizing foreign bodies, dead cells, and fragments of axons and myelin. Additionally, they release extracellular matrix proteins and cytokines that influence neuronal metabolism and regulate inflammation, immune responses, homeostasis, and promote axonal regeneration (Biswas and Mantovani, 2012; Chen et al., 2015a, 2015b, 2015c; Xu et al., 2021). Macrophages also recruit more of their kind through inflammatory signaling, participating in various stages of the inflammatory response to create favorable conditions for tissue regeneration (Fissel and Farah, 2021; Murray and Wynn, 2011). Typically, macrophages are categorized into two main phenotypes: M1 and M2. M1 Macrophages possess robust phagocytic capabilities that allow them to quickly clear debris from injured tissue, thereby providing a suitable microenvironment for subsequent repairs and promoting endothelial cell sprouting, proliferation, and migration during the early stages of angiogenesis.M2 Macrophages are more adept at tissue repair and can be further subdivided into four subtypes: M2a, M2b, M2c, and M2d. These subtypes are associated with promoting cellular proliferation, maturation, resolution of inflammation, and the stabilization and maturation of vasculature. Moreover, M2 macrophages are involved in processes such as antigen phagocytosis, clearance of foreign pathogens, transmission of danger signals, participation in memory cell formation, and remodeling of the myelin structure (Liu et al., 2019; Martin and García, 2021; Shimada et al., 2020; Wang et al., 2022). Understanding the dynamic roles and functions of these macrophage phenotypes is critical for developing therapeutic strategies that harness the regenerative potential of immune responses following nerve injuries.

4.1.2. Circulating macrophages homing to target tissues

Following peripheral nerve injury (PNI), resident macrophages (Mac) outside the myelin sheath are activated and release chemokines to recruit circulating macrophages (Ydens et al., 2020). These circulating macrophages respond swiftly, migrating to the injured site within a short timeframe (Benowitz and Popovich, 2011). Over time, they undergo phenotypic changes. In the initial stages post-injury, approximately within the first day, circulating macrophages at the injury site express both M1 and M2 related genes, although predominantly M1. Subsequently, within 3–5 days, they transition to an M2 phenotype, which facilitates the dominant phase of nerve repair (Dervan et al., 2021). Between days 2 and 7 post-injury, circulating macrophages also undergo significant proliferation, typically tripling the number of resident macrophage populations. Proliferation may peak between days 7 and 14, and by days 8 and 14, myelin clearance is usually completed, with elevated levels maintained for at least 30 days (Lindborg et al., 2018; Mokarram et al., 2012; Peluffo et al., 2015; Tomlinson et al., 2018), It has been reported that macrophages can persist in the distal segments of damaged nerves for at least six weeks (Kalinski et al., 2020). This sustained presence and dynamic transition of macrophages play a critical role in the debris clearance and subsequent regeneration phases following nerve damage.

4.1.3. Factors influencing macrophages in peripheral nerve injury

Peripheral Nerve Injury (PNI) triggers a cascade of pathophysiological responses such as neural tissue edema, ischemia, and inhibition of axonal transport (Y. Wang et al., 2015).The repair and regeneration following injury is a complex process involving inflammatory reactions, Wallerian degeneration, neovascularization, activation, proliferation, migration of Schwann cells (SCs), formation of Büngner bands, and elongation of neurites (Gao et al., 2013; Wieringa et al., 2018). The coordination between macrophages and SCs is crucial in this process (Zhang et al., 2022). Post-injury, macrophages rapidly migrate to the injured area, sensing changes in the local microenvironment. They secrete factors like VEGF-A to alleviate hypoxia, which in turn influences the functions of SCs. Concurrently, distal SCs, upon disconnection from the proximal axons, undergo significant changes in their signaling environment, transitioning to a dedifferentiated state. They phagocytize axonal and myelin debris and secrete a variety of cytokines to recruit more macrophages (Cattin et al., 2015; Stratton et al., 2017; Yi et al., 2020). In a rat model, recruited macrophages exhibit both pro-inflammatory and reparative phenotypes; pro-inflammatory macrophages converge on inflamed tissues to clear damaged cells, while reparative phenotype macrophages promote tissue regeneration (Mokarram et al., 2017). During the tissue repair process, besides SCs secreted cytokines that promote macrophage recruitment, several other conducive factors also facilitate the recruitment of macrophages to the target tissues, which collectively contribute to nerve regeneration. In summary, following PNI, the neural tissue undergoes various pathophysiological responses, initiating a series of complex repair processes. Macrophages play a key role in this context; they not only rapidly respond to injury, sense environmental changes, and secrete factors influencing SCs but also participate in debris clearance and tissue repair through different phenotypes. The cooperative efforts of SCs and various factors in promoting macrophage recruitment are crucial for nerve regeneration. Understanding the intercellular interactions and the factors influencing macrophage phenotypes is vital for enhancing repair after nerve damage (Table 2).

4.1.4. Coordination between macrophages and Schwann cells in peripheral nerve injury

Following peripheral nerve injury (PNI), during the degeneration phase, resident macrophages quickly detect changes in the microenvironment and rapidly release a plethora of cytokines, such as CCL2, TNFα, IL-1α, IL-1β. And monocyte-attracting chemokines (Chen et al., 2015a, 2015b, 2015c; Ydens et al., 2020). This process facilitates the recruitment of additional macrophages to the injury site. Concurrently, resident Schwann cells (SCs) detach from axons, losing their proximal signaling connections, and transition to a reparative phenotype. They work in coordination with macrophages to phagocytize and clear tissue debris (Huang et al., 2020; Kalinski et al., 2020; Stratton et al., 2017). In the regeneration phase, the interaction between macrophages and SCs exhibits time-dependent characteristics. SCs secrete neurotrophic factors such as Nerve Growth Factor (NGF) and Brain-Derived Neurotrophic Factor (BDNF), express adhesion molecules and integrins, and construct the basement membrane to support and guide axonal sprouting. Additionally, SCs synthesize components of the extracellular matrix (ECM) to facilitate axonal extension, providing direction and adhesiveness for neurite growth. Simultaneously, SCs secrete cytokines to promote the recruitment and precise phenotypic transition of macrophages. In turn, macrophages provide regenerative signaling molecules that promote SC activation and ECM remodeling (Ehmedah et al., 2020; Fissel and Farah, 2021; Huang et al., 2024). Macrophages also support the axonal regeneration mediated by "repair type" Schwann cells and

Table 2
Multiple cytokines affect macrophage recruitment, proliferation, differentiation, migration, apoptosis, and axon regeneration.

Protein and Gene	Signaling pathways	functional role
Collagen VI	AKT and PKA pathways	Promotes macrophage migration and polarization (Chen et al., 2015a, 2015b, 2015c)
TSG-6	NF-κB/NLRP3 axis	Regulates the polarization of macrophages (C. Li et al., 2022)
let-7b (microRNA)	let-7b/TLR4/NF-κB/STAT3/AKT	Mediates macrophage polarization and inflammation resolution (Ti et al., 2015)
RhoA (Ras homolog family member)	RhoA/ROCK/MLCK pathway	Affects macrophage migration and phagocytic capability (Alawieh et al., 2021)
L-PGDS	Non-cell autonomous mechanisms	Regulates macrophage phagocytic activity and accumulation (Forese et al., 2020)
CCR2	ccl2-ccr2 signaling pathway	Recruitment and migration of macrophages (Siebert et al., 2000)
Saa1 and Saa3	IL-6-SAA-CCL2signaling pathway	Enhances macrophage infiltration (Jang et al., 2012)
P-selectin		Mediates macrophage infiltration (Liou et al., 2013)
SIRT6		Affects macrophage migration, phagocytosis, and polarization (Zou et al., 2021)
CD300f		Regulates macrophage aggregation and phenotypic changes (Peluffo et al., 2015)
TNFα、IL-6和IL-1β		Impacts macrophage recruitment and clearance of myelin debris (Huang et al., 2020)
IL-17B/IL-17RB		Mediates macrophage recruitment (Ehmedah et al., 2020; Huang et al., 2024)
VEGF		Secreted by macrophages and regulates neovascularization and axonal regeneration (Ydens et al., 2020)
Plexin-B2		Enables macrophages to avoid axonal growth cones (Li, Kang, et al., 2022)
MCT1		Influences macrophage metabolism, phenotype, and functionality (Jha et al., 2021)

TSG-6: TNF-stimulated gene 6; L-PGDS: prostaglandin D2 synthase; CCR2: C-C-type biochemical receptor 2; Saa1 and Saa3: serum amyloid A1 and A3; SIRT6: silent information regulator 6; CD300f: CD300 molecule-like family member f; IL-17B: interleukin-17B; VEGF: vascular endothelial growth factor; MCT1: monocarboxylate transporter protein 1.

regulate the maturation of SCs by releasing growth-arrest-specific protein 6 (Gas6). Furthermore, macrophages express neuromodulatory proteins to promote myelination (Büttner et al., 2018; Wofford et al., 2022). In summary, during the degenerative and regenerative phases following PNI, the coordination between macrophages and SCs is crucial for nerve repair. Macrophages recruit additional immune cells by releasing pro-inflammatory cytokines and collaborate with SCs, which have transitioned to a reparative phenotype, to clear tissue debris. In the regenerative phase, SCs promote axonal extension by releasing growth factors and synthesizing ECM components, while also secreting cytokines to regulate the recruitment and function of macrophages. Macrophages provide regenerative signaling molecules, support SC activation and axonal regeneration, and regulate SC maturation by releasing specific factors like Gas6 and expressing neuromodulatory proteins to promote myelination. Understanding these interactions and coordination mechanisms is vital for comprehending the repair processes following nerve injury and developing new therapeutic strategies.

4.2. Neutrophils in peripheral nerve injury

Neutrophils play a crucial role in the regeneration and repair processes following peripheral nerve injury. Due to their high motility and sensitivity to chemotactic factors, neutrophils can rapidly extravasate into the injury site (Nadeau et al., 2011). At the site of injury, the primary functions of neutrophils include the release of reactive oxygen species (ROS) and lysosomal enzymes to eliminate pathogens and clear necrotic tissue. Additionally, neutrophils are closely associated with anti-tumor activities, immune responses, and tissue healing (Jerome et al., 2022). Moreover, neutrophils secrete proteins that are beneficial for nerve regeneration. For instance, they can produce neutrophil peptides, which are linked with tissue healing, recruitment of mononuclear macrophages, and nerve regeneration. Neutrophils can also secrete nerve growth factors, further connecting them to neural repair processes (Balog et al., 2023). In the context of peripheral nerve injury, neutrophils undergo rapid and complex metabolic changes. They participate in the clearance of inhibitory myelin and axonal debris, especially the immature neutrophil subpopulation expressing $Ly6G^{low}$ $CD14^{high}$, creating favorable conditions for subsequent regeneration processes (Sas et al., 2020; X. F. Zhao et al., 2022). Recent studies suggest that intermittent fasting can induce the gut microbiome to release indole-3-propionate, a metabolite that enters the bloodstream and can alter neutrophil phenotypes, ultimately benefiting nerve regeneration (Serger et al., 2022). However, it is important to note that excessive or prolonged inflammatory responses can lead to chronic inflammation, which may negatively impact nerve regeneration. Given the limited research in this area, the specific mechanisms of action of neutrophils in the peripheral nervous system are not fully understood and require further investigation.In summary, neutrophils play multiple roles in the regeneration and repair of peripheral nerve injuries. They clear damaged tissue through the release of ROS and lysosomal enzymes and promote nerve regeneration by secreting proteins such as nerve growth factors and neutrophil peptides. While neutrophils have a positive role in nerve regeneration, excessive or prolonged inflammatory responses could also have adverse effects. Thus, a deeper understanding of the mechanisms of action of neutrophils in the peripheral nervous system is crucial for developing new therapeutic strategies for nerve injury.

5. Interaction between vascular cells and perineural cells

Vascular cells play a crucial role in both the physiological and pathological processes of the nervous system. Their interactions with perineural cells form a complex and finely regulated network, primarily involving vascular endothelial cells (ECs), vascular smooth muscle cells, pericytes, and other cellular components of the Neurovascular Unit (NVU). In the early stages following neural injury, approximately within the first two days, ECs transition to a regenerative state, initiating reconstruction, activation, budding, and remodeling processes (Sun et al., 2024; Wang et al., 2017; Wynn and Vannella, 2016). During this phase, ECs secrete soluble factors that maintain the proliferation and differentiation of neural stem cells and produce Brain-Derived Neurotrophic Factor (BDNF) to stimulate neurite growth; Concurrently, they release Vascular Endothelial Growth Factor (VEGF) to promote angiogenesis (Lavasani et al., 2011; Meng et al., 2022; Ramos et al., 2015). The formation of new blood vessels precedes neural regeneration, providing essential oxygen and nutrients to damaged axons and non-neuronal cells, and stimulates their participation in establishing a microenvironment conducive to neural regeneration (Caillaud et al., 2019; Saffari et al., 2020; Zhou et al., 2019). While the precise mechanisms of interaction between ECs and other neural cells remain unclear, proteomic analysis of EC-derived exosomes (EC-Exo) has revealed various signaling pathways associated with angiogenesis and vascular function, such as Th1/Th2, Notch, and Protein Kinase A (PKA) signaling pathways (Wang et al., 2023). Research indicates that EC-Exo can enhance and maintain the phenotype, proliferation, migration, and

secretion of neurotrophic factors of Schwann cells (SCs) through activation of the PI3K/AKT/PTEN signaling pathway, thereby promoting nerve regeneration (Huang et al., 2023). Furthermore, EC-Exo can modulate the immune microenvironment by transferring ubiquitin-specific protease 13 (USP13) and protect neural cells from damage by inhibiting apoptosis (Ge et al., 2023; Xiao et al., 2017). In summary, the interactions between vascular cells and perineural cells are vital for the normal function, metabolic needs, and injury repair of the nervous system. Following nerve injury, endothelial cells quickly respond by secreting growth factors and soluble factors to promote the proliferation and differentiation of neural stem cells, while simultaneously stimulating angiogenesis and neurite growth. Proteomic analysis of exosomes has revealed potential mechanisms of interaction between vascular cells and other neural cells, including enhancing the functionality of SCs and modulating the immune environment through the activation of specific signaling pathways. Understanding these interactions is crucial for developing new strategies to promote repair after neural injury.

6. Interaction between fibroblasts and perineural cells

Fibroblasts (Fbs) play a critical role in the peripheral nervous system. Originating from neural crest cells, they are responsible for synthesizing the extracellular matrix (ECM), which varies in structure, biomechanical properties, and function across different organs, also filling tissue defects (Hara et al., 2023; Plikus et al., 2021; Y. Zhao et al., 2022). For instance, in the development and regeneration of the nervous system, Fbs derived from sensory and motor neural stem cells can express proteins with diverse biological characteristics (He et al., 2023). During nerve regeneration, fibroblasts engage in significant regulatory interactions with neurons and Schwann cells (SCs). Neural fibroblasts (N-Fbs) provide a conducive microenvironment for neuronal regeneration and secrete activin A to promote the proliferation and migration of SCs (B. Chen et al., 2021; Li, Cheng, et al., 2022). Fbs can also express tenascin-C (TNC), a protein that directly binds with the β1 integrins expressed by SCs, regulating the direction and extension of neurites. This specific extension phenomenon is a result of precise coordination between Fbs and the neurites of neurons and SCs (He et al., 2023; Qu et al., 2021). The hepatocyte growth factor B/EphB2 signaling pathway between Fbs and SCs also mediates the directed migration of SCs, guiding axonal regeneration (Parrinello et al., 2010). Fibroblast-derived exosomes (exo) can promote the expression of myelin-related genes in SCs by targeting the TSC2/mTORC1/SREBP2 signaling axis, thereby mediating myelination (Y. Zhao et al., 2022). However, in inhibitory neural environments, exosomes secreted by Fbs can interact with other non-neuronal exosomes to regulate protein synthesis and axonal regeneration (Zhou et al., 2024). In summary, fibroblasts are pivotal in the development, maintenance, and regeneration of the peripheral nerves. They engage in complex interactions with neurons and SCs through the synthesis of ECM and secretion of various bioactive molecules, thereby regulating neurite growth and axonal regeneration. Exosomes secreted by Fbs also play a key role in promoting myelination and regulating protein synthesis. Understanding the interactions between fibroblasts and perineural cells is crucial for unveiling the mechanisms of neural regeneration and developing new therapeutic strategies.

7. Role of the extracellular matrix in neurophysiology

The extracellular matrix (ECM) is a natural material produced by animal organs and tissues, comprising a diverse array of microstructures and proteins with various functions (Prest et al., 2018). The tissue-specific components of the ECM make it an ideal cellular scaffold that participates in several physiological processes such as the transmission of mechanical forces, signal transduction, and the release of growth factors (Brown and Badylak, 2014; Sun et al., 2020). The insoluble components of the ECM provide physical support for axons, preventing signal interference between them (Barton et al., 2017). One of the components, glycosaminoglycans (GAGs), such as chondroitin sulphate and hyaluronic acid,enhances the hydration of the ECM, conferring structural stability to the tissues and protecting growth factors from proteolytic degradation (Neves et al., 2020). It has been demonstrated that the direction of growth of peripheral axons is directed by chondroitin sulfate-carrying proteoglycans (Liu et al., 2023). Hyaluronic acid has been demonstrated to play an important role in the proliferation, differentiation, and cell signaling of nerves (Huang et al., 2021). GAGs (heparin and heparan sulfates) can also regulate biological processes by binding with fibroblast growth factors (FGF) (Malaeb et al., 2019; Xu and Esko, 2014). Therefore, the ECM serves as a complex repository of structural and functional proteins that can reshape the intracellular environment and guide cell phenotype, survival, and behavior (Kim et al., 2020). It is evident that a symbiotic relationship exists between the extracellular matrix (ECM) and cells, whereby both entities benefit from the coexistence (Kaul and Ventikos, 2015). In the peripheral nervous system, the ECM is primarily synthesized and secreted by Schwann cells, with over 90 % composed of collagen. This collagen not only provides structural support but also mediates biological processes through intracellular signaling, forming the basis for axonal and Schwann cell regeneration (Chen et al., 2015a, 2015b, 2015c). During nerve regeneration, proteins within the ECM (Laminin-1, laminin-2, and fibronectin) promote neural regeneration, provide mechanical support for axons, and participate in regulating the cell biology of Schwann cells (Motta et al., 2019). In summary, the extracellular matrix (ECM) plays a crucial role in neurophysiology. It acts not only as a physical scaffold for cells but also participates in cellular signaling and the regulation of growth factors. The tissue-specific nature and complex protein composition of the ECM make it a critical regulator of cellular behavior. In the peripheral nerves, the ECM synthesized by Schwann cells provides foundational support and resources for axonal support and regeneration. Understanding the structure and function of the ECM is vital for revealing mechanisms of neural regeneration and developing new therapeutic strategies for nerve injuries.

8. Conclusion and prospects

In summary, the cellular ecology of the peripheral nervous system constitutes a complex ecosystem driven by interactions among various cell types and the microenvironment. In this system, neuroglial cells (especially Schwann cells), immune cells, vascular endothelial cells, fibroblasts, and neuronal cells play pivotal roles. They interact through intercellular signaling, cellular movement, and the chemical and physical properties of the microenvironment, collectively maintaining the normal function of the nervous system.

The ecological changes in cells following peripheral nerve injury represent a complex process influenced by multiple factors. The release of neurotrophic factors, the regulation of inflammatory and immune responses, and the formation of new blood vessels are critical in modulating this process. A deep understanding of these repair mechanisms is essential for developing new therapeutic strategies. Recent advances in treating nerve injuries using stem cells, exosomes, growth factors, genetic, and pharmacological interventions have shown promising results. Nevertheless, finding more effective treatment methods remains a focus of ongoing research efforts.Future research directions should further explore: the signaling mechanisms that activate the reparative phenotypes of Schwann cells (SCs) post-nerve injury; strategies to control aging in SCs; mechanisms to recruit local and circulating macrophages, lymphocytes, and neutrophils; methods to regulate macrophage polarization; ways to mediate coordinated interactions among cells within the ecosystem; utilization of the blood-nerve barrier and the complement protein system; improvements in local metabolism, including mitochondrial respiration and glycolysis; the roles of different cell types in nerve injury repair; studies on how adjusting the cellular

ecology can enhance nerve injury repair and regeneration; and the use of emerging technologies such as stem cells and gene editing to promote the repair and regeneration of nerve injuries.

Ethical statement

It is hereby declared that the English article under consideration has been written in accordance with the highest standards of ethical conduct. The content is entirely original and has been crafted through diligent research, thoughtful analysis, and creative expression, with scrupulous avoidance of any form of plagiarism. All ideas, arguments, and data presented are the intellectual property of the author. Extensive research was conducted using a wide array of reputable sources. In instances where the work of others has been referenced, it has been done so with the utmost respect and with proper citation. Each source has been meticulously acknowledged, giving due credit to the original authors and their contributions. This approach not only upholds the integrity of academic and intellectual discourse but also allows readers to trace the lineage of ideas and verify the information provided. Furthermore, a balanced and unbiased perspective has been striven for in the article. I have endeavoured to ensure that my writing is free from any form of discrimination or prejudice based on personal characteristics such as race, gender, religion, nationality, and so on. The language employed is respectful and inclusive, with the aim of fostering a constructive and open-minded dialogue among readers. I am aware of the importance of ethical writing in maintaining the credibility of my work and contributing positively to the broader community of scholars and readers. By adhering to these ethical principles, it is hoped that trust and confidence in the article will be inspired, and that others will be encouraged to uphold similar standards in their own writing. No conflicts of interest were reported in relation to this study.

CRediT authorship contribution statement

Limao Wu: Writing – original draft, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Jinglan He:** Writing – review & editing, Supervision, Project administration, Investigation, Funding acquisition. **Na Shen:** Writing – review & editing, Supervision, Project administration, Investigation. **Song Chen:** Writing – review & editing, Project administration, Funding acquisition.

Founding

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Conflicts of Interest

No conflicts of interest were reported in relation to this study.

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