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GENETIC AND MOLECULAR MECHANISMS ASSOCIATED WITH PERIPHERAL NERVE REGENERATION AND VASCULAR REPAIR

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ABSTRACT

Peripheral nerve regeneration and vascular repair are closely interconnected biological processes that are essential for restoring tissue structure and function following injury. Effective regeneration depends on coordinated cellular and molecular responses involving Schwann cells, endothelial cells, immune cells, and extracellular matrix components. This review summarizes the major genetic and molecular mechanisms that regulate peripheral nerve regeneration and vascular repair, with particular emphasis on Wallerian degeneration, Schwann cell reprogramming, axonal regeneration, and angiogenesis. Key genetic regulators, including transcription factors and neurotrophic molecules, are discussed alongside the roles of non-coding RNAs and epigenetic modifications in controlling regenerative responses. The review further examines neurovascular crosstalk, highlighting how interactions between neural and vascular systems contribute to tissue remodeling and functional recovery. Shared signaling pathways, including PI3K/Akt, MAPK/ERK, JAK/STAT, Notch, TGF-β/Smad, and HIF-1α/VEGF, are explored as central regulators of both nerve and vascular regeneration. In addition, emerging therapeutic strategies involving gene-based interventions, stem-cell therapies, extracellular vesicles, and tissue-engineered biomaterials are evaluated for their potential to enhance regenerative outcomes. Collectively, current evidence demonstrates that successful tissue repair relies on the integration of neural and vascular regenerative mechanisms. A deeper understanding of these interconnected molecular networks may facilitate the development of targeted therapies capable of improving functional recovery and advancing regenerative medicine.

KEYWORDS: Peripheral nerve regeneration; Vascular repair; Neurovascular crosstalk; non-coding RNAs; Regenerative signaling pathways

1. INTRODUCTION

Peripheral nerve injuries (PNIs) are a major clinical problem worldwide, occurring at a high incidence in millions of people annually and frequently leaving patients with sensory, motor, and pain abnormalities and low quality of life. The peripheral nervous system has a greater capacity to regenerate after injury than the central nervous system, but complete functional recovery after severe injury to the peripheral nervous system is still challenging. There are several factors including the degree of axonal damage, microenvironment, rate of axonal regrowth and timely re-establishment of contacts with target tissues, that affect the regenerative outcome. As a result, nerve repair response mechanisms are a hotspot of research in the fields of regenerative medicine and molecular neuroscience (Liu & Duan, 2023; Chu et al., 2022).

Peripheral nerve regeneration is a well-orchestrated biological event at the cellular, molecular and genetic level that is aimed entirely at repairing tissues and restoring function. After nerve injury, a series of processes start to occur, such as Wallerian degeneration, Schwann cell activation, immune cells infiltration, ECM remodeling, and axonal regeneration. Schwann cells are especially important in this process, as they become phenotypically reprogrammed into repair-supportive cells that promote clearance of debris, provide neurotrophic factors, and direct growth of regenerating axons toward their targets. At the same time, transformations of bio-mechanical and biochemical properties of the regenerative microenvironment greatly affect cellular behaviors and the efficiency of regeneration (Kong et al., 2022; Ye et al., 2022).

In recent years, our knowledge of the genetic networks and signaling pathways governing peripheral nerve regeneration has been greatly expanded thanks to advances in molecular biology and genomics. Many of the genes, transcription factors,

growth factors, and signaling pathways associated with regeneration have been identified as being critical in neuronal survival, Schwann cell plasticity, axonal extension, and tissue remodeling. Specifically, transcriptional regulation has become a focal point for determining success of regeneration, with myriad intricate gene expression programs regulating the shift from injury response to functional recovery. These findings have helped to uncover the molecular mechanisms underlying nerve regeneration and have identified potential therapeutic targets that could be used to improve the outcomes of nerve regeneration (Zhang et al., 2023; Ye et al., 2022).

Besides neural repair mechanisms, there is growing evidence of the critical role of vascular repair in effective tissue regeneration. The newly formed blood vessels deliver oxygen, nutrients, growth factors and cellular support that are essential to maintaining the regenerative processes. Angiogenesis and vascular remodeling contribute to tissue survival after injury, as well as provide an environment conducive to the growth of axons and function of Schwann cells. Recent research indicates that there are complex neurovascular interactions between neural and vascular systems, with endothelial cells, immune cells and neural cells working together to coordinate tissue repair and regeneration. This is now a recognized phenomenon of neurovascular coupling and has broadened the historical definition of peripheral nerve repair, which has traditionally focussed on the neurone, and highlighted the need for integrated regenerative networks.

Moreover, recent progress in regenerative medicine has also speeded up the creation of novel approaches to better nerve repair. Tissue-engineered nerve grafts, biomaterial based scaffolds, electrical stimulation strategies and biologically active interventions have all shown promise in promoting axonal regeneration and functional recovery. Increasingly, these strategies involve modulation of molecular signalling pathways and genetic regulators involved in tissue repair processes, which now allow for a connection between basic biology and translation (Li et al., 2024; Yang et al., 2023).

Since there are now many lines of evidence that suggest overlapping mechanisms for genetic regulation, molecular signaling and vascular remodeling in tissue repair, it is important to understand the mechanisms involved in regenerating peripheral nerves and repairing vessels to develop effective regenerative therapies. It is therefore the aim of this review to highlight the state of knowledge on the genetic and molecular mechanisms involved in peripheral nerve regeneration and vascular repair, focusing on cellular responses, regulatory genes, signaling pathways, neurovascular interactions and emerging molecular targets that might help to facilitate improved regeneration.

2. Peripheral Nerve Regeneration: Cellular and Molecular Basis

2.1 Wallerian Degeneration

Wallerian degeneration is the first biological response to an injury of the peripheral nerve and lays the groundwork for the regeneration of the damaged nerve. After the axons are disrupted, the distal nerve segment becomes fragmented and the myelin breaks down, causing the removal of damaged cell components. This process forms a "regenerative microenvironment", which is conducive to the continued repair of nerves. The degree to which Wallerian degeneration is successful depends on the extent of the injury, the age of the individual and their metabolic state, which influence the regeneration outcomes (Dahlin, 2023). One of the key elements of this process is the co-ordinated action of Schwann cells and macrophages. Schwann cells change to a repair phenotype and help clear debris, and infiltrating macrophages help remodel tissue and clear molecules that might be inhibitory for regeneration. Their interaction is important for the shift from degeneration to regeneration and plays a crucial role in functional recovery after peripheral nerve injury (Wu et al., 2024). Moreover, the signaling of transforming growth factor beta (TGF-β) is involved in regulation of inflammatory response, extracellular matrix remodeling and Schwann-cell activity, which supports tissue degeneration to regeneration process (Ding et al., 2024).

2.2 Schwann Cell Reprogramming

Schwann cells are key players in peripheral nerve regeneration. Following injury, they are phenotypically reprogrammed to a repair-supportive state, in which they promote neuronal survival and axonal guidance, and tissue remodeling. This property of plasticity is unique to the peripheral nervous system and plays an important role in the ability to recover (Jiang et al., 2024). Schwann cells' interactions with the extracellular matrix, which supplies structural support and biochemical signals to influence Schwann cell migration, proliferation, and differentiation, are important to their regenerative functions. Such interactions can help establish regeneration pathways that direct axonal growth towards distal targets (Jiang et al., 2024). In addition, microRNAs also influence Schwann-cell behavior by controlling gene-expression networks involved in Schwann-cell proliferation, migration and myelination. These molecules, through post-transcriptional regulation, are important to coordinate cellular responses during the repair process (Borger et al., 2022). Macrophage–Schwann cell communication also is a central issue in regeneration. Macrophages release cytokines, chemokines, and growth factors that have a variety of effects on Schwann-cell activity and tissue remodeling, supporting the regenerative microenvironment needed for successful nerve repair (Wu et al., 2024).

2.3 Axonal Regeneration

After creating a favorable environment for regeneration, damaged axons start to regenerate by growth-cone formation, cytoskeletal reorganization, and guidance signals. Successful axonal regeneration relies on coordinated interactions between neurons, Schwann cells, components of the extracellular matrix and molecular signaling pathways directing the axons back towards their original targets (Hu et al., 2023). There are a number of systemic causes affecting the efficiency of regeneration. By affecting tissue homeostasis, inflammation and cellular metabolism, chronic inflammatory and metabolic diseases, especially diabetes, can disrupt nerve repair. This is because these changes typically lead to slow regeneration and incomplete functional recovery (Zhao et al., 2024; Espino-Gonzalez et al., 2024). On the other hand, physical activity induces pathways that lead to tissue remodeling and cell survival and the production of growth factors,

helping the recovery process (Chen et al., 2022). The neurovascular interactions in the course of regeneration are also emerging as important. Good vascular support brings in nutrients, oxygen and signalling molecules that are important for growth of the axons and repair of the tissues. Thus, the neurovascular coupling is an important mechanism by which the neural and vascular systems work together to improve regenerative outcomes (Qin et al., 2022).

3. Genetic Regulators of Peripheral Nerve Regeneration

3.1 Activating Transcription Factor 3 (ATF3)

Activating transcription factor 3 (ATF3) is among the most widely studied transcription factors in peripheral nerve regeneration that are activated by injury. AFT3 is immediately induced at high levels in damaged neurons after nerve injury, and serves as a molecular switch that stimulates programs of gene-expression in neurons that promote regeneration. ATF3 modulates genes involved in stress adaptation, survival and axonal growth, which help establish a pro-regenerative environment to facilitate functional recovery. ATF3 is strongly associated with the signalling pathways that are triggered by injury and is a marker of positive regeneration in the peripheral nervous system. Additionally, many molecular mechanisms involved in regeneration process, including stem cell-mediated repair and tissue engineering, converge to promote neuronal regeneration and remodeling through ATF3 (Li et al., 2024; Hu et al., 2023).

3.2 c-Jun Signaling

c-Jun is one of the transcription factors which are activated following peripheral nerve injury and is a primary transcription factor that regulates the plasticity and regeneration of Schwann cells. High expression of c-Jun favors the transition of mature Schwann cells to repair-supportive variants that can help in the clearance of debris, in trophic support and in axonal guidance. c-Jun's role in Schwann cells is not limited to their regulation and is involved in other cellular responses linked to tissue repair, inflammatory regulation and metabolic adaptation. New findings indicate that mitochondrial homeostasis and cellular stress-response pathways play an important role in influencing regenerative outcomes by modifying the interaction(s) with transcription factors like c-Jun. These interactions help to sustain the viability and regenerative competence of cells after nerve injury (Chang et al., 2023; Peña & Martin, 2024).

3.3 SOX10-Mediated Schwann Cell Regulation

SOX10 is a transcription factor that helps maintain the identity of Schwann cells, and regulates the expression of genes involved in myelination. SOX10 is involved in the dedifferentiation and redifferentiation of Schwann cells during peripheral nerve regeneration, which is necessary for the remyelination of the nerves by Schwann cells. Regulation of Schwann cell phenotypes is critical to re-establish nerve conduction and for long-term functional recovery. In recent years, it has become apparent that Schwann cell communication is crucial not only with other Schwann cells, but also with neighboring cellular populations such as endothelial cells, and the constituents of the neurovascular niche. These interactions help regulate the networks of regenerative genes and facilitate a synchronized neural and vascular tissue-repair response (Huang et al., 2024; Tao et al., 2023).

3.4 Growth-Associated Protein 43 (GAP43)

Growth-associated protein 43 (GAP43) is known as a molecular marker of axonal regeneration and neuronal plasticity. The expression of GAP43 has been shown to be closely linked to active elongation of axons and growth cone formation, and is, therefore, commonly found in situations where these processes occur. GAP43 is important for the structural changes involved in nerve extension and reinnervation of targets, and thus is directly involved in functional recovery following nerve injury. Several neurotrophic and growth-associated signaling pathways, such as insulin-like growth factor-1 (IGF-1), which has become a key factor in the regulation of neuronal survival and regenerative abilities in both physiologic and pathological contexts, regulate the expression of GAP43 (Arjunan et al., 2023).

3.5 Neurotrophic Factors

Another large group of genetic regulators controlling peripheral nerve regeneration are neurotrophic factors. Neurotrophic molecules like nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), and glial cell line-derived neurotrophic factor (GDNF) are important for cell communication, neuronal survival, axonal extension and synaptic plasticity during the entire regeneration process. A complex regulation of the expression of these factors is tightly controlled by complex transcriptional and epigenetic mechanisms that react dynamically to tissue damage. The recent discovery of chromatin biology has shown that the accessibility of chromatin and epigenetic remodeling play important roles in the transcription of regeneration-associated genes and growth-promoting factors. Chromatin remodeling mechanisms can regulate access to specific genomic regions and are important in coordinating the activation of molecular pathways required for tissue repair and regenerative success. Overall, these findings underscore the significance of integrated genetic regulatory systems in regulating peripheral nerve regeneration and functional recovery (Chen et al., 2024; Li et al., 2024).

Table 1. Major Genetic Regulators of Peripheral Nerve Regeneration

Genetic Regulator	Primary Function	Contribution to Regeneration	Source
ATF3	Injury-responsive transcription factor	Promotes neuronal survival and activation of regenerative gene-expression programs	Li et al. (2024); Hu et al. (2023)

c-Jun	Regulator of Schwann cell plasticity	Facilitates repair phenotype formation, inflammatory regulation, and axonal support	Chang et al. (2023); Peña & Martin (2024)
SOX10	Schwann cell differentiation factor	Maintains Schwann cell identity and supports remyelination	Huang et al. (2024); Tao et al. (2023)
GAP43	Growth-associated protein	Supports axonal elongation, growth cone formation, and neuronal plasticity	Arjunan et al. (2023)
Neurotrophic Factors (NGF, BDNF, GDNF)	Growth-promoting signaling molecules	Enhance neuronal survival, axonal growth, and regenerative capacity	Chen et al. (2024); Li et al. (2024)

4. Molecular Mechanisms of Vascular Repair

4.1 Angiogenesis Following Injury

Angiogenesis is an important aspect of vascular repair to restore oxygen and nutrients to damaged tissue. After injury, endothelial cells get activated due to hypoxia and inflammatory signals, leading to the development of new vessels. These processes help the tissue to survive and help to encourage the tissue to regenerate. Angiogenesis efficiency can be influenced by multiple physiological factors, such as age, metabolic status and inflammatory conditions, affecting the regenerative outcomes (Pu et al., 2023; Summer et al., 2024).

4.2 Endothelial Cell Activation and Migration

Activation of endothelial-cells is an early key event in vascular repair. Activated endothelial cells proliferate, migrate and re-organize to make new vascular networks to restore tissue perfusion. Macrophages play a major role in this process as they produce cytokines and growth factors which activate endothelial responses and vascular remodeling. Thus, the crosstalk between endothelial cells and immune cells is crucial for orchestrating the repair and regeneration of tissues (Rehman et al., 2024; Chen et al., 2024).

4.3 Pericyte Recruitment and Vessel Stabilization

Stability of newly formed vessels requires endothelial cell/vascular cell (pericyte) interactions. These interactions control blood vessel functioning, permeability, and integrity in the long run. Dysregulated redox reactions lead to a disruption of endothelial function and cell communication, which negatively affect vascular repair, while redox balance promotes tissue regeneration. Thus, regulation of ER stress also plays a role in cellular adaptation and survival, which is important for maintaining the homeostasis in vascular system and promoting successful repair (Leyane et al., 2022; Chen et al., 2023).

4.4 VEGF Signaling Pathway

The vascular endothelial growth factor (VEGF) pathway is the major control pathway in regulating angiogenesis and vascular remodeling. VEGF promotes endothelial-cell proliferation, migration, and survival, and the formation of functional vascular networks. Beyond VEGF signalling, other metabolic pathways like AMPK/PGC-1α/PPAR-γ affect inflammatory, angiogenic and regenerative responses. These pathways help in tissue repair by controlling cellular metabolism and immune function. In addition, PPARα signaling plays a role in regulating endothelial function and vascular homeostasis via its influence on oxidative stress and inflammatory regulation, thus presenting therapeutic prospects in the area of regenerative medicine (Zhou et al., 2023; Pu et al., 2023).

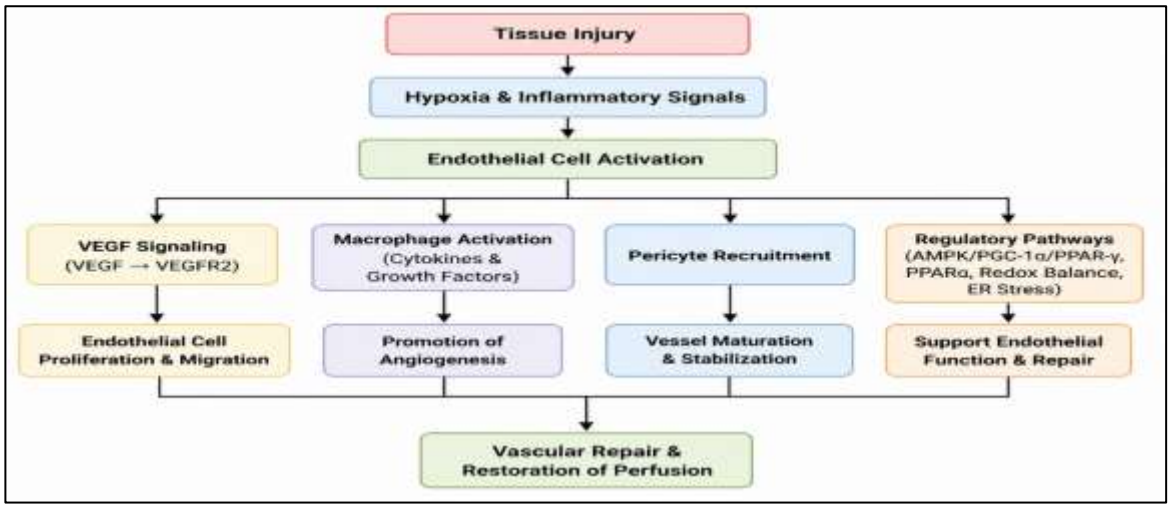

Figure 1. Molecular mechanisms governing vascular repair and angiogenesis.

Table 2. Key Molecular Mediators of Vascular Repair

Molecular Mediator	Primary Function	Role in Vascular Repair	Source
VEGF	Endothelial growth factor	Stimulates angiogenesis and vascular remodeling	Pu et al. (2023); Zhou et al. (2023)

Macrophages	Immune regulators	Promote endothelial activation and tissue repair	Chen et al. (2024)
AMPK/PGC-1α/PPAR-γ Pathway	Metabolic signaling pathway	Regulates inflammation and regenerative responses	Zhou et al. (2023)
PPARα	Nuclear receptor	Maintains endothelial function and vascular homeostasis	Pu et al. (2023)
Oxidative Stress Regulators	Redox homeostasis mediators	Influence vascular remodeling and endothelial survival	Leyane et al. (2022)
Endoplasmic Reticulum Stress Pathways	Cellular stress-response systems	Regulate endothelial adaptation and tissue repair	Chen et al. (2023)
Endothelial Cell Signaling Networks	Cellular communication systems	Coordinate angiogenesis and vascular reconstruction	Rehman et al. (2024); Summer et al. (2024)

5. Neurovascular Crosstalk During Tissue Repair

5.1 Blood Vessel-Guided Axonal Regeneration

The coordinated restoration of vascular networks is also required for successful tissue regeneration in addition to the neural repair. After peripheral nerve injury, the formation of new blood vessels often directs the regrowth of these nerves towards damaged target tissues both structurally and biochemically. The tight anatomic and functional relationship between regenerating nerves and vessels has prompted the discovery of neurovascular crosstalk as one of the basic elements of regenerative biology. Blood vessels deliver oxygen, nutrients, growth factors, and components of the extracellular matrix, all of which contribute to a conducive microenvironment for neuronal survival and extension of the axons. Furthermore, vascular networks can be used as migratory channels of supportive cells for regeneration, thereby increasing the efficiency of regeneration. Using neurotrophic and proangiogenic factors in therapy has additionally shown that simultaneous stimulation of neural and vascular regeneration has a profound effect on recovery after peripheral nervous system injury (Idrisova et al., 2022). Recent molecular studies have shown that vascular associated transcriptional regulation is essential for maintaining communication between the neural and vascular compartments. Changes in gliovascular signaling networks may impact vascular permeability, cellular communications, and tissue homeostasis and hence regenerative responses. These results indicate that regulation of neural and vascular systems is integral in successful tissue repair and functional restoration (İş et al., 2024).

5.2 Endothelial-Derived Growth Factors

Endothelial cells contribute to tissue regeneration through production of growth factors and signals that control cellular survival, growth, migration, and differentiation. During vascular remodeling, such signals play an important role in blood vessel and neural repair by contributing to a favorable regenerative environment. The presence of neurotrophic and proangiogenic factors secreted by endothelial cells promotes axonal growth, Schwann cell activity, and tissue remodeling, indicating that vascular and neural regeneration have close relations (Idrisova et al., 2022). Bioactive compounds in nature influence the function of endothelial cells and the process of angiogenesis. Among them are plant polyphenols that provide vasoprotection, antioxidant, and anti-inflammatory effects which promote vascular and neural regeneration.

5.3 Schwann Cell–Endothelial Cell Interactions

Schwann cells and endothelial cells play significant roles in the process of neurovascular healing. Schwann cells play an important role in providing trophic support to aid in axonal regeneration, ECM modulation, and axonal guidance, whereas endothelial cells provide support to neurons through vascularization. The interactions of Schwann cells and endothelial cells with various signaling molecules lead to the creation of a conducive environment for neurovascular regeneration. Rejuvenation processes, such as increased repair capacity, metabolic adaptability, genomic stability, and stress response regulation, play a crucial role in promoting cellular regeneration and can enhance Schwann-endothelial communication for neurovascular regeneration (Ji et al., 2023).

5.4 Immune Modulation of Neurovascular Repair

The immune system plays an important role in the process of neurovascular repair, directing processes like inflammation, remodeling, and regenerative signaling. Inflammation needs to be controlled as its excessive levels may disrupt the process of healing. Therefore, the regulation of immune cell activity is crucial for adequate tissue restoration. Electrical stimulation contributes to enhanced repair through the modulation of cellular signaling, neuroplasticity, and inflammation, having an effect on various pathways associated with the improvement of neurologic processes, as well as vascular responses and regeneration environment. As a result, the process of repair benefits from better coordination between vascular and neuronal elements (Dorrian et al., 2023). Metabolic regulation can also influence neurovascular repair mediated by the immune response. For example, alterations in the lipid metabolic pathway and subsequent changes in signaling can influence inflammatory and remodeling processes, as well as neurovascular regeneration (Shi et al., 2024).

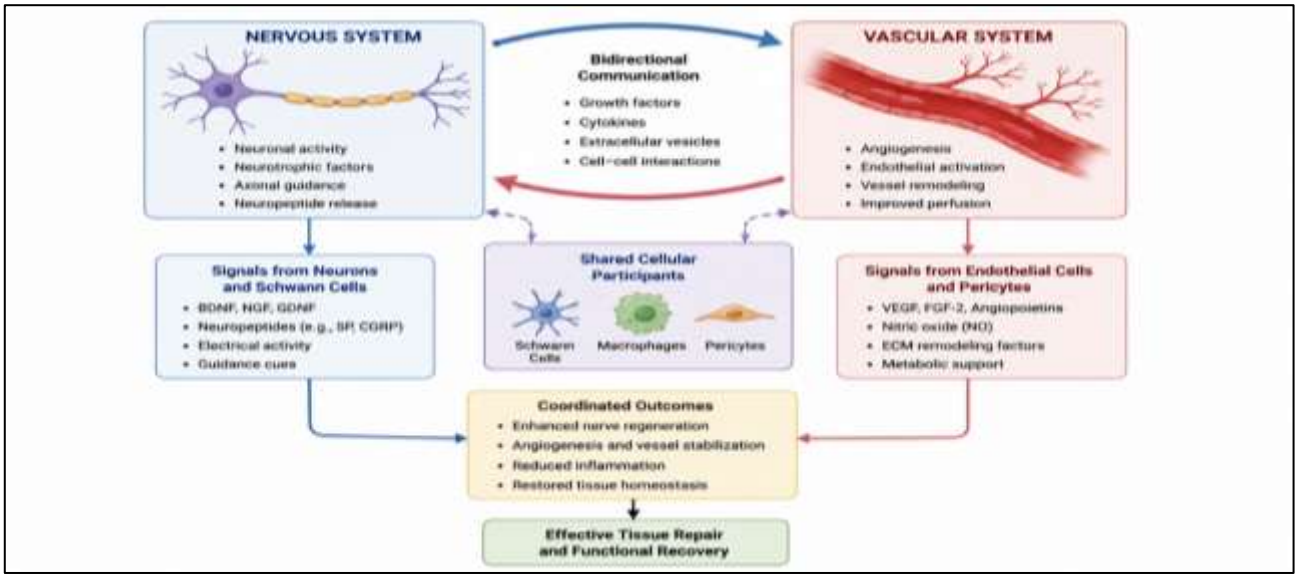

Figure 2. Neurovascular crosstalk during tissue repair and regeneration.

Table 3. Key Cellular Mediators Involved in Neurovascular Repair

Cellular Mediator	Primary Function	Contribution to Neurovascular Repair	Source
Endothelial Cells	Vascular remodeling and angiogenesis	Provide growth factors, nutrients, and regenerative signals	Idrisova et al. (2022); Froldi & Ragazzi (2022)
Schwann Cells	Axonal guidance and trophic support	Promote nerve regeneration and tissue remodeling	Ji et al. (2023); Idrisova et al. (2022)
Blood Vessels	Structural and metabolic support	Guide axonal growth and maintain tissue homeostasis	İş et al. (2024); Idrisova et al. (2022)
Immune Cells	Inflammatory regulation	Coordinate tissue remodeling and regenerative responses	Dorrian et al. (2023); Shi et al. (2024)
Neurotrophic and Proangiogenic Factors	Cellular signaling mediators	Simultaneously enhance neural and vascular regeneration	Idrisova et al. (2022)
Gliovascular Networks	Neural–vascular communication systems	Regulate tissue integrity and regenerative signaling	İş et al. (2024)

6. Role of non-coding RNAs and Epigenetic Regulation

6.1 MicroRNAs

MiRNAs are tiny RNA molecules which control gene expression in a post-transcriptional manner and are involved in the process of repair, tissue differentiation, and regenerative signaling. In peripheral nerve and vascular repair, miRNAs affect cell proliferation, ECM remodeling, and inflammation via influencing several target genes at once. MiRNAs have been shown to be linked to excess fibrosis and ineffective tissue repair when expressed dysregulated, indicating their vital role in keeping regenerative balance after injuries (Garcia Garcia et al., 2023).

6.2 Long Non-Coding RNAs

LncRNAs control gene expression via a variety of transcriptional and post-transcriptional processes. Such molecules take part in the process of adaptation, regulation of inflammation, and tissue remodeling via their interactions with DNA, RNA, and proteins. Recent studies have provided support for the involvement of lncRNAs in regulating regenerative response by altering signaling pathways responsible for vascular, neuronal regenerations, and immune cell functioning (Constantinescu-Bercu et al., 2023).

6.3 Circular RNAs

CircRNAs are extremely stable RNAs which play a role in regulating gene expression and communication between cells. The interaction of circRNAs with miRNAs and regulatory proteins makes them responsible for neuronal survival, axon growth, and tissue remodelling. Biomaterial regenerative strategies might have an impact on the cellular network signalling pathways involving circRNA function and improve peripheral nerve regeneration (Wang et al., 2022).

6.4 Histone Modifications and DNA Methylation

Epigenetic mechanisms include histone modifications and DNA methylation. They have been found to regulate chromatin structure and gene expression through the control of gene access. As such, these mechanisms have been noted to affect regeneration due to their roles in controlling the expression of inflammatory, cell flexibility, and healing genes. Epigenetic control regulates several processes in relation to regeneration, such as the regulation of glia cell activity,

neuroinflammation, and adaptive reactions after cell damage (Lu & Gao, 2023). Moreover, any kind of treatment based on the use of stem cells requires the regulation of various epigenetic control mechanisms which affect cellular renewal and differentiation into specific lineages. The way cells are regulated determines their role in tissue regeneration. Hence, there is a connection between epigenetic control mechanisms and effective tissue regeneration (Szymoniuk et al., 2022).

Table 4. Non-Coding RNAs and Epigenetic Regulators Associated with Regeneration

Regulator	Primary Function	Contribution to Regeneration	Source
MicroRNAs (miRNAs)	Post-transcriptional gene regulation	Modulate tissue repair, fibrosis, and regenerative signaling pathways	Garcia Garcia et al. (2023)
Long Non-Coding RNAs (lncRNAs)	Transcriptional and post-transcriptional regulation	Regulate inflammation, cellular adaptation, and tissue remodeling	Constantinescu-Bercu et al. (2023)
Circular RNAs (circRNAs)	Gene-expression modulation and molecular signaling	Influence neuronal survival, cellular communication, and tissue repair	Wang et al. (2022)
Histone Modifications	Chromatin remodeling and transcriptional control	Regulate inflammation, neural plasticity, and regenerative responses	Lu & Gao (2023)
DNA Methylation	Epigenetic gene regulation	Controls stem-cell differentiation and regenerative potential	Szymoniuk et al. (2022)

7. Signaling Pathways Shared by Nerve and Vascular Regeneration

7.1 PI3K/Akt Signaling Pathway

Phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) pathway plays an important role in regulating cell survival, proliferation, metabolic processes, and repair. Peripheral nerve regeneration involves the stimulation of neuronal cell survival and axonal elongation by the PI3K/Akt pathway, while in vascular tissue, it improves the survival of endothelial cells and angiogenic responses. Moreover, the PI3K/Akt pathway helps in maintaining the regenerative and stem-cell functions by regulating cellular adaptability towards injury and stress. The impact of aging on the PI3K/Akt pathway activity has been associated with poor regenerative potential (Montazersaheb et al., 2022).

7.2 MAPK/ERK Signaling Pathway

The MAPK/ERK pathway is responsible for controlling cellular growth, differentiation, and regeneration. After injury, activation of this pathway promotes neuron survival, Schwann cells functioning, endothelial cell proliferation, and remodeling of the extracellular matrix. Additionally, the MAPK/ERK pathway operates as one of the key factors mediating growth factor–mediated cellular signaling, allowing the tissue to react adequately to the regenerative signals. Therefore, the MAPK/ERK pathway acts as one of the most significant pathways connecting development with neurovascular repair (Jha et al., 2022).

7.3 JAK/STAT Signaling Pathway

JAK/STAT pathway, on the other hand, has been identified as an important pathway in controlling inflammatory response, immune cell functions, and regeneration. Inflammation triggered by the JAK/STAT pathway as a consequence of tissue damage not only impacts cell survival but also affects tissue remodeling. In addition to that, this pathway also coordinates the communication process between immune and regenerative cells. While a controlled JAK/STAT signaling process helps in tissue repair, sustained activation might cause chronic inflammation and tissue dysfunction.

7.4 Notch Signaling Pathway

The notochord signaling pathway has been shown to be highly conserved and plays a critical role in cell fate specification and differentiation. In the context of tissue regeneration, it plays a role in modulating the function of neural progenitor cells, vascular cells, and other supportive cell types. Effective activation of the Notch pathway is crucial for the process of tissue reconstruction and cellular plasticity, while aberrant activation can hinder the regenerative process (Jha et al., 2022).

7.5 TGF-β/Smad Signaling Pathway

Transforming growth factor-beta (TGF-β)/Smad signaling regulates extracellular matrix remodeling, cellular differentiation, fibrosis, and immune responses. During tissue repair, this pathway contributes to regeneration by controlling cellular migration, matrix deposition, and inflammatory regulation. Although moderate activation supports healing, excessive signaling can promote pathological fibrosis and compromise tissue function. Thus, precise regulation of TGF-β/Smad signaling is necessary for maintaining a balance between tissue repair and excessive scarring (Andronie-Cioara et al., 2023).

7.6 Wnt/β-Catenin and HIF-1α/VEGF Signaling

Wnt/β-catenin and hypoxia-inducible factor-1 alpha/vascular endothelial growth factor (HIF-1α/VEGF) signaling pathways play essential roles in controlling regenerative biology. The Wnt/β-catenin pathway regulates cell division, cell differentiation, and stem cell survival, whereas the HIF-1α/VEGF signaling pathway stimulates angiogenesis during

hypoxic conditions. These signaling pathways work together to promote vascular remodeling, endothelial cell survival, and regeneration of tissues after damage. Inadequate functioning of endothelium cells is closely related to reduced regenerative capacity and is often the result of changes in angiogenic signaling. Activation of the VEGF signaling pathway increases endothelial cell survival and vascular remodeling, along with restoring blood flow to injured tissues. Moreover, zinc-dependent signaling mechanisms play an important role in cardiovascular homeostasis and are responsible for signaling involved in vascular repair (Tsigkou et al., 2023; Hara et al., 2023).

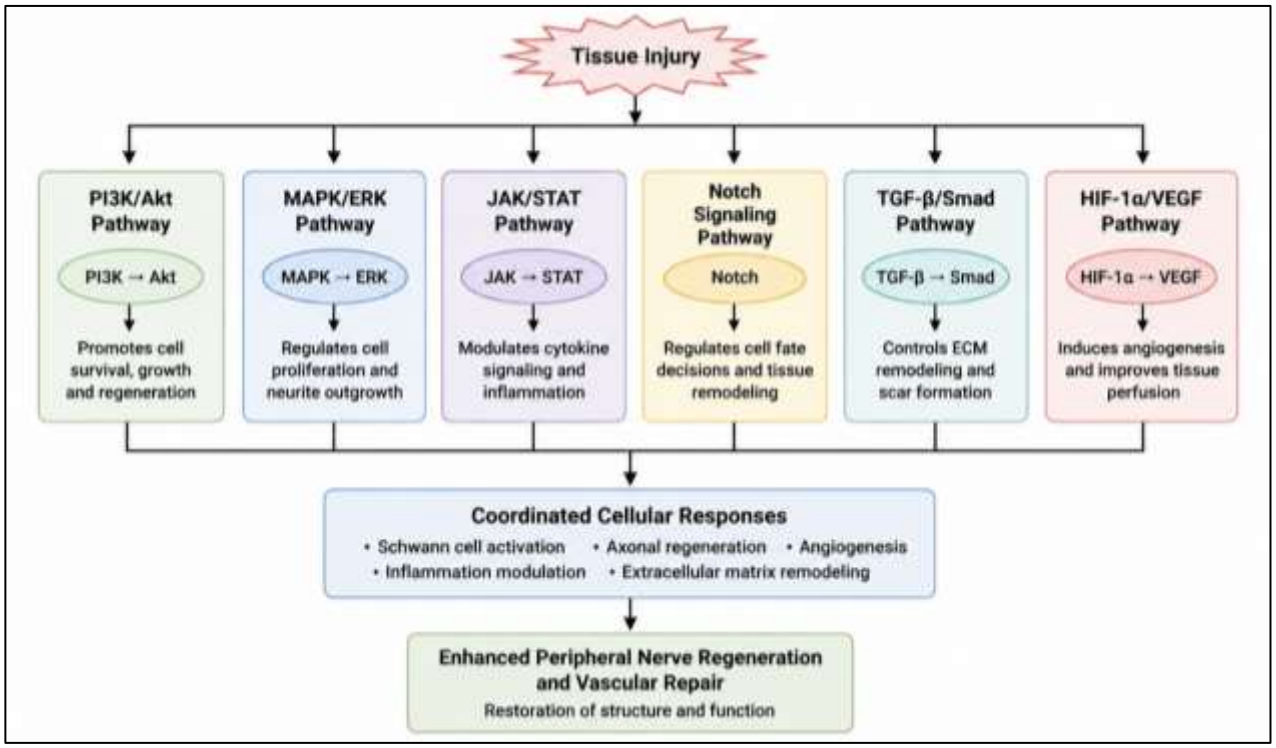

Figure 3. Integrated signaling pathways regulating peripheral nerve regeneration and vascular repair.

Table 5. Shared Signaling Pathways Involved in Nerve and Vascular Regeneration

Signaling Pathway	Primary Biological Function	Contribution to Regeneration	Source
PI3K/Akt	Cell survival and metabolic regulation	Promotes neuronal survival, angiogenesis, and stem-cell maintenance	Montazersaheb et al. (2022)
MAPK/ERK	Cellular growth and differentiation	Enhances neural repair, endothelial proliferation, and tissue remodeling	Jha et al. (2022)
JAK/STAT	Cytokine-mediated signaling	Regulates inflammation, immune responses, and regenerative gene expression	Andronie-Cioara et al. (2023)
Notch	Cell-fate determination and differentiation	Controls cellular plasticity and tissue reconstruction	Jha et al. (2022)
TGF-β/Smad	Extracellular matrix remodeling and fibrosis regulation	Supports tissue repair and immune modulation	Andronie-Cioara et al. (2023)
Wnt/β-Catenin	Cellular proliferation and stem-cell regulation	Maintains regenerative capacity and tissue renewal	Jha et al. (2022)
HIF-1α/VEGF	Hypoxia adaptation and angiogenesis	Promotes vascular repair and endothelial regeneration	Tsigkou et al. (2023); Hara et al. (2023)

8. Therapeutic Applications and Future Perspectives

Emerging knowledge of the genetic and molecular basis of peripheral nerve regeneration and vascular repair have made it possible to develop new regenerative therapies. Although surgical and rehabilitative methods are important, they frequently do not achieve full functional recovery after extensive tissue damage. Thus, more and more focus has been placed on biologically targeted interventions designed to promote the regeneration of neural and vascular tissue, through modulation of cellular and molecular processes. Gene-based therapies have great promise in enhancing the regenerative outcome through the control of the genes associated with neuronal survival, axonal growth, angiogenesis, and tissue repair. Likewise, stem-cell-based methods have proven to be attractive strategies, because they can contribute to tissue reconstruction and generate a microenvironment with regenerating properties by secreting bioactive molecules. These therapies can encourage the growth of new blood vessels and nerves to improve cell-to-cell communication, lower

inflammation, and promote tissue remodeling. The attention has also been brought to cell-free therapeutic platforms such as extracellular vesicles and exosomes. Their molecular cargo can affect cellular behavior and their ability to promote tissue repair, while bypassing some drawbacks of direct cell transplantation. Concurrently, tissue engineering has evolved to allow the generation of scaffolds and nerve conduits that promote cellular attachment, migration and differentiation using biomaterials. The biomaterials can also be used to transport regenerative molecules, making tissue regeneration more efficient. New technologies like multi-omics, precision medicine and Artificial Intelligence are likely to continue reshaping regenerative medicine. Combination of genomic, transcriptomic, proteomic and metabolomic data could help in the identification of novel biomarkers and therapeutic targets and help in developing personalized treatment strategies. Furthermore, computational methods can help to enhance the ability to predict regenerative outcomes and design therapies. While significant progress has been made, significant challenges remain concerning safety, durability, regulatory acceptance and clinical translation. So further interdisciplinary studies will be needed to move from the molecular to therapeutic applications. These efforts may eventually lead to the establishment of more effective methods to promote peripheral nerve regeneration and vascular repair.

9. CONCLUSIONS

Peripheral nerve regeneration and vascular repair are complex genetic, molecular, and cellular processes that are closely organized. Multiple events must occur such as Schwann cell reprogramming, axonal regrowth, angiogenesis, immune modulation and extracellular matrix remodeling for successful tissue regeneration. These have been driven by recent advances which have greatly enhanced our understanding of the regulatory network controlling these processes, and in which transcription factors, signaling pathways, non-coding RNAs, and epigenetic mechanisms play an important part in determining the regenerative outcome. The increasing knowledge of the neurovascular interaction has further highlighted the need to consider neural and vascular regeneration in the same context. Rather, coordinated communication between neurons, Schwann cells, endothelial cells, immune cells and other components of the regenerative microenvironment is necessary for effective tissue repair. This link-grafted view opens new possibilities for the design of therapeutic approaches which can address neural and vascular repair mechanisms at once. Due to ongoing advances in molecular biology, regenerative medicine, tissue engineering and precision therapeutics, it is hoped that increasingly effective interventions for tissue repair will be developed in the near future. Insights into the common pathways underlying peripheral nerve regeneration and vascular repair could aid in the search for new therapeutic targets and help to enhance clinical outcomes. In the future, combining the genetic and molecular information with translational approaches will be crucial for further developing regenerative therapies.

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