Chapter

Schwann Cell Plasticity in Peripheral Nerve Regeneration after Injury

Emilia Manole, Alexandra Eugenia Bastian, Ana Maria Oproiu, Monica Teodora Neagu, Carolina Constantin and Gheorghita Isvoranu

Abstract

In the normal peripheral nervous system, Schwann cells (SCs) are present in two different states of differentiation: myelinating SCs that surround large-caliber axons, forming myelin sheath, and non-myelinating SCs that surround more small-caliber axons forming Remak bundles. Under pathological conditions (injury or inflammation), SCs, with a remarkable plasticity, undergo phenotypic transformations, downregulating the production of myelin proteins mRNAs, upregulating neurotrophic factors and cytokines, thus promoting the axonal regeneration. Dedifferentiated SCs activate the protein degradation, participating in the demyelination process and clearance of myelin debris; attract macrophages helping wound healing; proliferate to replace lost cells; guide axonal growth; and protect against secondary axonal damage. Thus, SC functions have a critical contribution to regeneration processes that occur in peripheral nerve after injury.

Keywords: Schwann cell plasticity, dedifferentiated Schwann cells, peripheral nerve regeneration, myelin recovery

1. Introduction

Schwann cells (SCs) are glial cells present in the peripheral nerve system (PNS). The name was given in honor of the German scientist Theodore Schwann, who discovered them in the nineteenth century [1] although they were not the main subject of his research. At that time it was thought that this type of cells is very complex and that the cells merge to supply peripheral nerves. Ramon y Cajal, only about 100 years later, discovered the true structure of the peripheral nerves, composed of axons and SCs that are in a symbiotic connection with it [2]. In the following years, with the evolution of electron microscopy, the study of SC morphology has developed continuously, leading to a better understanding of their complex biology.

It is known that nerves in PNS are much easier to regenerate than those in the central nervous system (CNS). Ramon y Cajal sensed very well that there is a "symbiosis" between the axon and the Schwann cells. Kidd et al. [3] described the Schwann cell as one of the largest and most complex cells in the body, which can develop and evolve rapidly after injury. The origin of the Schwann cell is in the

neural crest, and this differentiation is made by the regulation of Sox10 but also in the presence of Notch and endothelin signaling [4, 5].

After a peripheral nerve lesion, a series of cellular changes occur at both axons and Schwann cells, a phenomenon known as Wallerian degeneration: axonal degeneration and myelin destruction, followed by a dedifferentiation (an immature-like phenotype of SCs) and proliferation of Schwann cells [6].

The purpose of this chapter is to highlight the extremely important role of the Schwann cell in the regeneration of the peripheral nerve and its extraordinary plasticity in order to ensure this phenomenon.

2. Peripheral nerve injury

What does peripheral nerve injury mean? This could mean a mechanical trauma, transection or crush, or a pathological condition, when could be affected sensory nerves, motor nerves or autonomic nerves. A peripheral neuropathy may affect one or many nerves, axon, or myelin in the first stage.

In the nerve transection, all nerve fibers are affected, while in a disease manifestation, only a number of nerve fibers are affected, others being normal (**Figures 2A** and **4**).

Very briefly, in peripheral neuropathies, it may be an axonal primary damage or a myelin sheath primary damage. After a period both components of the nerve fiber are affected.

Primary axonal degeneration, whether it is nerve transection or a pathological manifestation, is essentially the same: it starts with a Wallerian degeneration in the distal part of nerve (**Figure 1**), following the myelin destruction. On semithin transverse

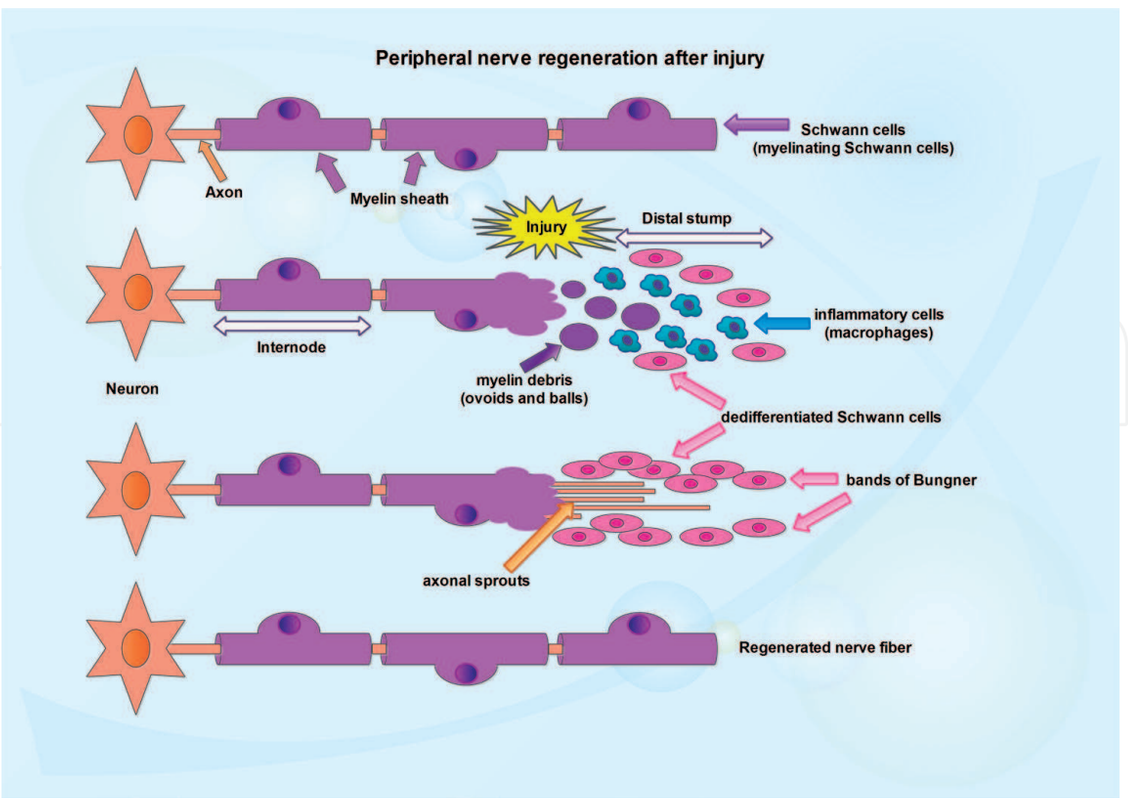

Figure 1.
Wallerian degeneration. After injury, axon and myelin sheath in the distal stump degenerate. Macrophages migrate to the site of lesion and with proliferating Schwann cells remove myelin debris. After the debris has been removed, dedifferentiated Schwann cells align forming bands of Bungner, guiding axonal sprout regeneration.

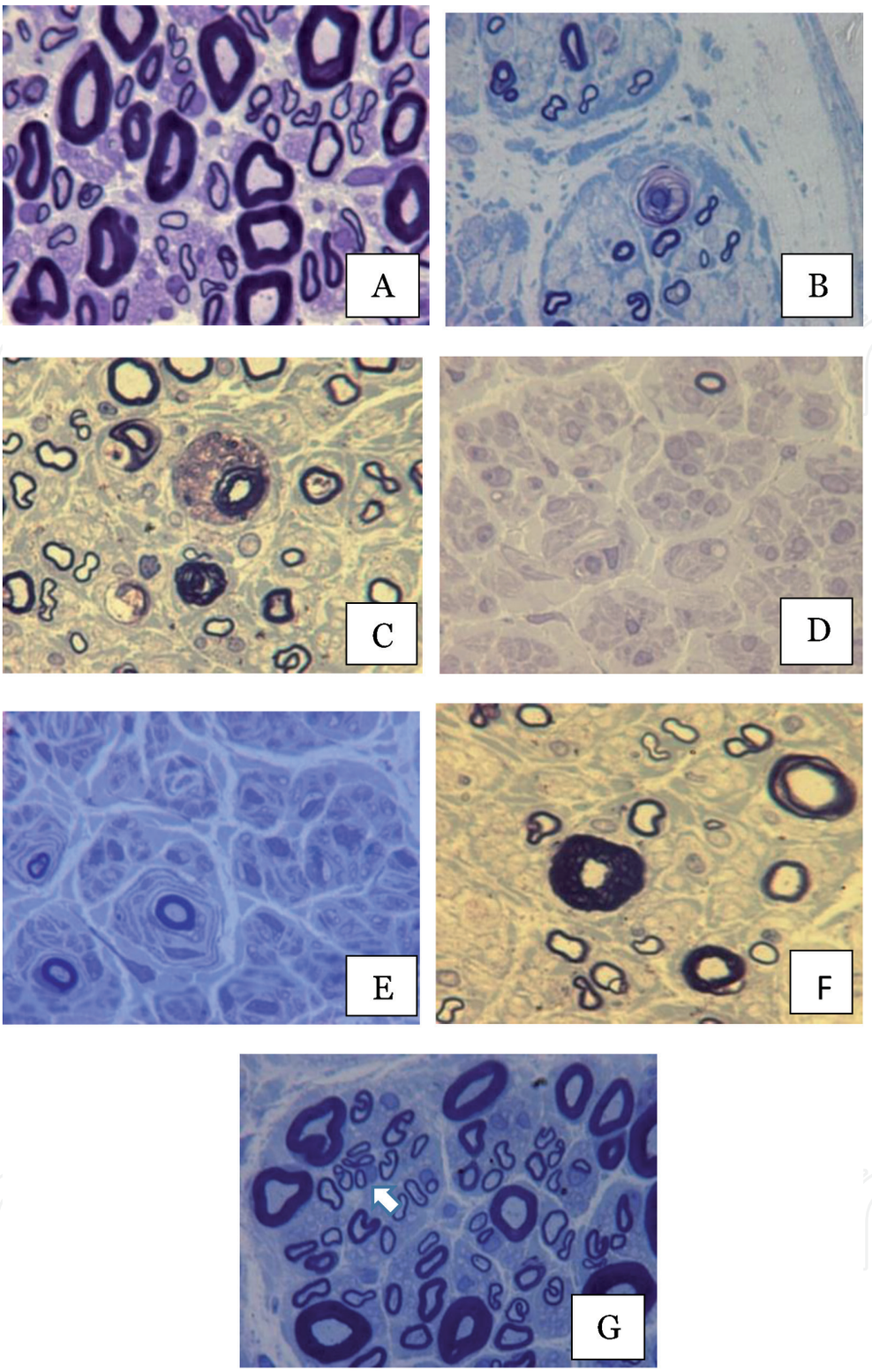

Figure 2.
Peripheral nerve pathological modifications (sural nerve biopsy): (A) a very mild affected nerve, with a normal fiber density; some myelinated fibers with small and medium mean diameter with demyelination; (B) a severe axonal destruction, with disappearance of many large diameter axons and with a low-fiber density; a degenerated axon is present; (C) many degenerated axons and demyelination present in the rest of myelinated fibers; (D) a very severe neuropathy with disappearance of most of the myelinated fibers; (E) some small myelinated axons with onion bulbs; (F) a hypermyelinated fiber in an HNPP case (tomacula) in the center of the image; (G) regeneration aspect: cluster of small axons (arrow). Semithin cross sections stained with toluidine blue; (under oil immersion – 60× Objective).

sections (**Figure 2B** and **C**) and in electron microscopy images (**Figure 3**), the affected nerve fibers are seen to be in a process of necrobiosis. In electron microscopy images, autophagic vacuoles are seen, near the axon (**Figure 3A**) or in the exterior layer of SC,

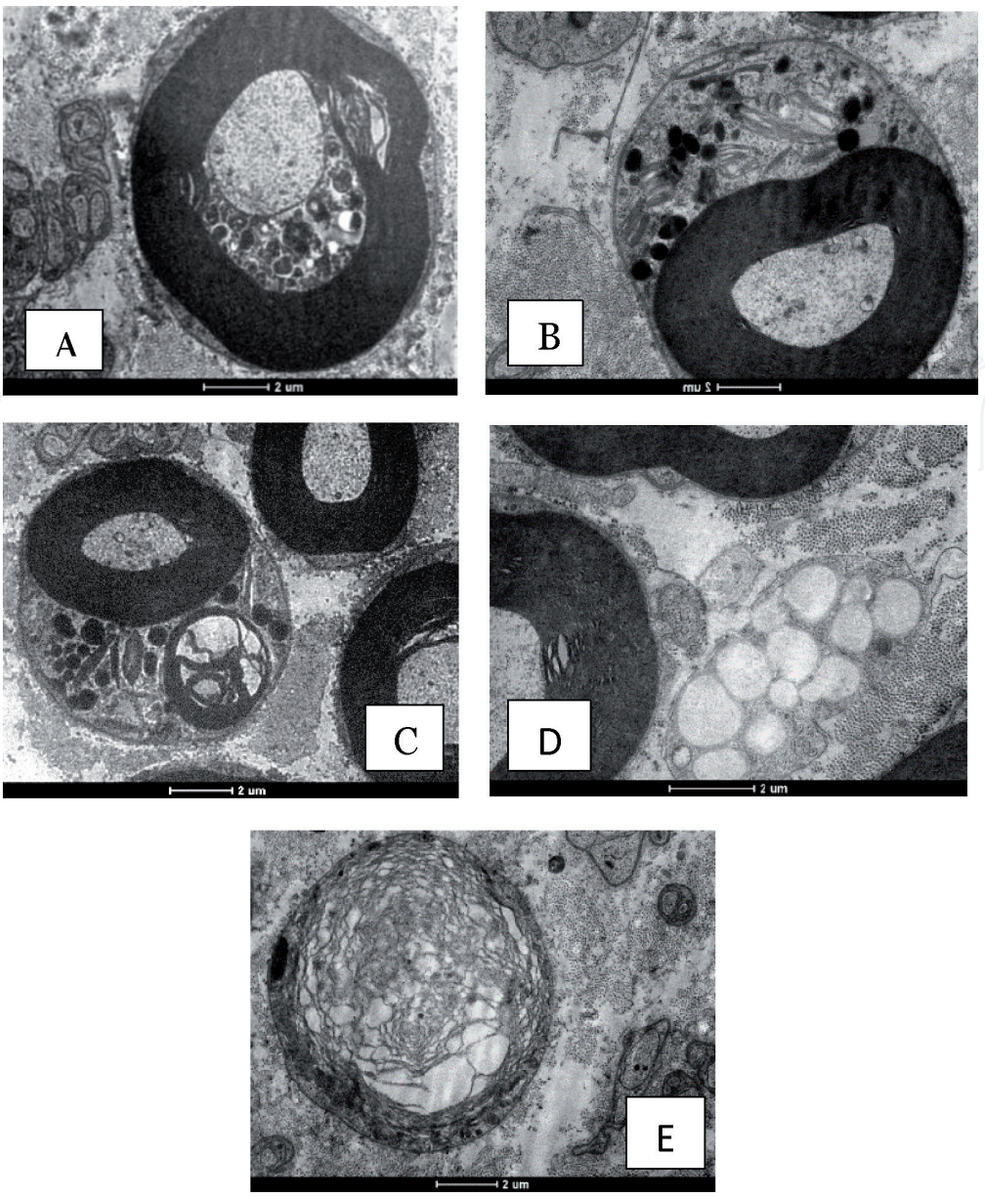

Figure 3.
Electron microscopy aspects of axonal degeneration (sural nerve biopsy). (A) A myelinated axon showing an autophagic vacuole between axon and myelin sheath. (B) A myelinated axon with an autophagic vacuole in the Schwann cell exterior cytoplasma: small myelin debris are seen. (C) The same aspect: an autophagic Schwann cell with many smaller or bigger fragments of myelin inside. (D) A macrophage with lipid droplets is present near myelinated axons. (E) Total myelin degradation; only irregular laminated structure is present, with no axon (cross sections; bar = 2 μm).

under the basal lamina (**Figure 3B** and **C**) and macrophages (**Figure 3D**). After the destruction of the nerve fiber, only irregular structures of myelin residues can be seen (**Figure 3E**) or myelin debris like ovoids and balls (**Figure 4B** and **C**). If it is a chronic process, many nerve fibers disappear, the density of myelinated fibers being very low (**Figure 2D** and **E**). When the myelin is affected in the first step, not all Schwann cells are suffering in the same time. One internode with a very thin sheath between two normal internodes may be observed: segmental demyelination (**Figure 4A** and **B**). When a myelin protein, PMP22, is genetically affected, in hereditary neuropathy with pressure palsies (HNPP), the nerve biopsy shows demyelination and focal hypermyelination structures, tomacula (sausage-like) (**Figures 2F** and **4D**). In hypertrophic neuropathies, like Charcot-Marie-Tooth disease type 1A (CMT 1A) and chronic inflammatory demyelinating polyneuropathy (CIDP), some structures named "onion bulbs" are present, a result of concentric layers of Schwann cell processes and collagen around the axons (**Figure 2E**). It is a repetitive segmental demyelination and myelin regeneration.

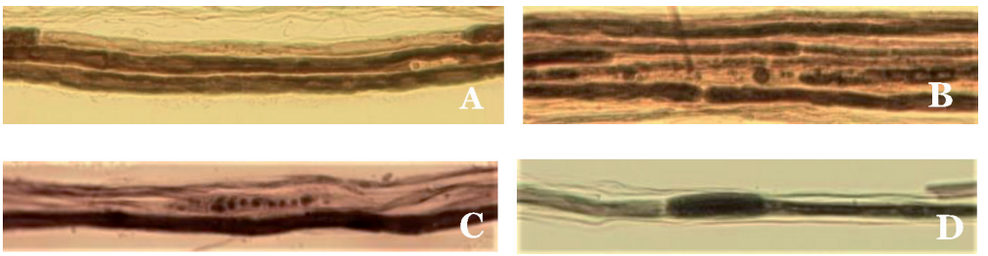

Figure 4.
Teased nerve fiber (sural nerve biopsy) panel. (A) A nerve fiber with segmental demyelination near two other normal myelinated fibers. (B) Near normal fibers, a fiber with segmental demyelination (a thin internode) and a fiber with few myelin ovoids and balls (axonal degeneration). (C) More myelin ovoids in an axonal degeneration. (D) A tomacula in myelin sheath of a nerve fiber.

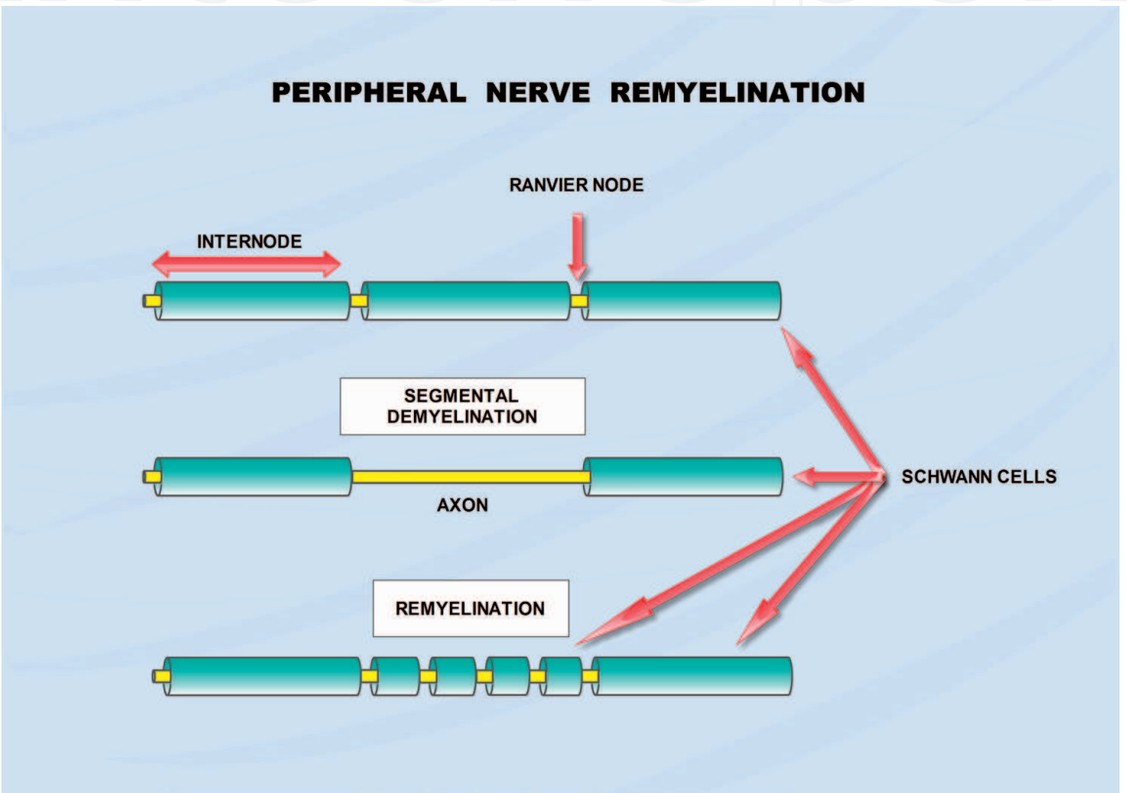

Figure 5.
Peripheral nerve remyelination. In demyelinating peripheral neuropathies, the segmental demyelination is often seen. Following a Schwann cell degeneration, the lost myelin internode is replaced by some Schwann cells which generate myelin sheaths, resulting in many shorter internodes.

After a segmental demyelination, along the affected internode, several Schwann cells arrive which begin to remyelinate this portion, the sign of remyelination being more short internodes (**Figure 5**).

The sign of axonal regeneration is observed on semithin sections and consists of the presence of some clusters of axons with the same small mean diameter and thinner myelin sheath (**Figure 2G**).

After these images sowing just few aspects of pathological degradation of peripheral nerve, focusing on myelin sheath damage, let's take a closer look at what happens in the Schwann cell, at the cellular and molecular level.

3. Myelin protein gene expression in peripheral nerve after injury

Investigating the evolution of the main proteins that enter the composition of myelin sheath during and after nerve injury has been a subject of study for many

scientists. These proteins are P zero (P_0), myelin basic protein (MPZ), and P2. The first two play an important role in maintaining the integrity and compactness of the myelin sheath. P2 is a lipid-binding protein and participates in fatty acid elongation and transport during the myelination process [7]. Myelin associated glycoprotein (MAG) is a transmembrane protein that is found in the periaxonal region and participates in SC-axon contact organization. It seems to be involved in the myelination process after injury [8]. P_0 and MBP mRNA in the distal nerve portion after transection were found to be 20% lower than normal levels but have had normal levels after crushing [9, 10]. In the absence of a contact between SCs and the axon, the levels of mRNAs of P_0 and MBP remained low, and mRNA of MAG was undetectable, long time after nerve transection, whereas MAG mRNA was undetectable after lesion; in the case of a crush injury, after a sudden and short decrease, the mRNA levels of these proteins were found to increase rapidly afterwards [10, 11].

4. Biological aspects of Schwann cell

To understand what plasticity of Schwann cells means, we need to understand what the starting point is for their differentiation and evolution.

4.1 Schwann cell differentiation and development

During development, SCs surround bundles of axons and support them to outgrow by releasing growth factors such as nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), brain-derived neurotrophic factor (BDNF), and neurotrophin (NT3) [12–14]. It follows a "radial sorting" of axons by extension of cellular process from Schwann cells, which begins to divide axon bundles into smaller ones and finally separate the neighboring axons with cell cytoplasm. Thus two types of fibers are formed: (i) unmyelinated Remak fibers, in which SC surrounds several small-sized axons (sensory and autonomic) and does not produce myelin, and (ii) myelinated fibers in which each large-sized axon is surrounded by a SC cell, 1:1 relationship, and a myelin sheath is formed by SC membrane spirally wrapping the axon [15]. Mesaxon is termed the point where the plasma membrane apposition is formed where the first encircling process meets itself. Remak SCs maintain the proliferative capacity of all the life [16].

During this stage, changes in cell morphology and gene expression occur, mediated by the transcription factor Krox-20 (or Egr-2) [17–19].

4.2 Interactions between Schwann cells and axons

The differentiation of Schwann cells is controlled by some **growth factors** among which the most important are in the neuregulin family. Neuregulins (Nrgs) are transmembrane proteins that signal through ErbB tyrosine kinase receptors [20]. Axonal neuregulin-1 (Nrg1), produced in many isoforms by alternative splicing (heregulin, glial growth factor, sensory and motor neuron-derived factor), interacts with ErbB2/ErbB3 receptors tyrosine kinase expressed on Schwann cells [21–25]. ErbB2 and ErbB3 combine to act as heterodimers and efficiently bind Nrg1. **Nrg1/ErbB** signaling axis has a critical role in Schwann cell development (for review [26–28]) like survival, proliferation, migration, differentiation, and myelination [26, 29–32].

Nrgs need protease involvement for Nrg1-ErbB interactions because Nrgs are synthesized as single-pass transmembrane proteins and shed from the cell surface

by the proteolytic cleavage, thus permitting the interaction with ErbB receptors across the periaxonal space [33, 34].

Another enzyme implicated in Nrg1 cleavage is beta-amyloid converting enzyme (BACE1), a **beta-secretase** present in axon [35, 36]. An *in vivo* study showed that the BACE1-null mice presented reduced rates of Nrg1 cleavage and decreased PNS myelin, a low capacity of myelination with axons with a thinner myelin sheath [35].

An effect opposite to the BACE activity has tumor necrosis factor-alpha-converting enzyme (TACE), a neuronal alpha-secretase, cleaving Nrg1 into an inactive form [37]. TACE genetic inactivation in motor neurons caused hypermyelination like in Nrg1 overexpression.

Another factor that is essential in SCs-axon interaction, with a protection role for the axon, is **Schwann cell basal lamina**. The basal lamina together with extracellular collagen fibrils protects axons from extension and compression injuries. They provide good support for axonal outgrowth and guidance (reviewed by [38]). Basal lamina defines also Schwann cell orientation in axonal myelination [39]. More of this, SCs require axonal contact for secreting the components of basal lamina, so the relationship of axon-SCs via basal lamina is interactive and reciprocal [40, 41].

All these interactions described above are very important and may be modulated in the control of nerve regeneration.

5. Schwann cell plasticity

PNS has a very good regenerative capacity, and this is largely due to Schwann cells that develop a high plasticity and can contribute very quickly to the regeneration of peripheral nerves after injury whether it is a trauma or a pathological condition. In these cases, SCs have the ability to transform into an immature-like form, which drives subsequent regeneration of the nerve. These processes of dedifferentiation into non-myelinating cells and redifferentiation after injury are characteristic of these glial cells in PNS, and in the last decade a significant progress has been made in the study of the molecular mechanisms and signaling pathways that regulate this plasticity (reviewed in [42]). More of this, the myelinating and non-myelinating SCs remain bipotential cells all the time, as demonstrated by grafting or nerve cross anastomosis experiments [43–45]. Many experimental studies on transgenic animals have shown that after nerve cut or crush, both types of SCs reprogram into proliferative progenitor-like repair SCs [46, 47]. This phenomenon involves downregulation of pro-myelinating genes, such as early growth response 2 (Egr-2 or Krox-20), POU domain class 3 transcription factor 1 (Pou3f1 or Oct-6), and myelin protein zero (MPZ)/myelin basic protein (MBP). There is also an upregulation of markers of dedifferentiated (immature) SCs like low affinity neurotrophin receptor (p75NTR), c-Jun, or glial fibrillary acidic protein (GFAP) [6].

After Wallerian degeneration following nerve injury, a downregulation of pro-myelinating genes occurs, and the myelin clearing phenomenon begins after myelin sheath disorganization, through a mechanism of autophagy or myelinophagy [48]. Macrophages also participate in this process, phagocytosing myelin and axonal debris. The recruitment of macrophages is also done by SCs [49–51].

One of the major problems of human SCs is that as their regenerative capacity decreases in time, they can no longer sustain axonal growth, and their numbers decrease greatly (reviewed in [52]).

Regarding the plasticity of Schwann cells, although not covered by this chapter, we just want to mention here that SC precursors can generate many and different

cell types during embryogenesis, besides myelinating and non-myelinating SCs, such as endoneurial fibroblasts, melanocytes, and neurons [52].

5.1 Schwann cell dedifferentiation

After injury, SCs reacquire some capabilities from early development, like proliferation, production of growth factors, sorting, and myelination. A good review regarding the biology of Schwann cells is the one made by Kidd et al. [3].

SC behavior and fate is regulated by two sort of interactions: SCs-axon and SCs-extracellular matrix/basal matrix. After 48 hours following axonal transection, SCs downregulate the production of myelin protein mRNAs [53] and upregulate trophic factors and cytokines [12–14] like NGF, BDNF, GDNF, and LIF, molecules necessary in axonal regeneration promoting into distal stump (reviewed in [54]). After axonal injury/transection, the axon is rapidly destroyed by a nonapoptotic autonomous mechanism [55]. SCs begin myelin degradation after axon injury, disassembling first the myelin internode starting with Schmidt-Lantermann incisure swelling [56, 57], following the dissolution of myelin in bubbles, ovoids, and balls. Macrophages finish the myelin degradation by phagocytosis [58]. It is not known exactly how much the SCs contribute to myelin degradation compared to macrophage participation, but it seems that it depends on the volume of the internode [59, 60]. During myelin degeneration, changes occur in the SC microtubule network, lysosome, and endosome positioning [61].

After nerve crush or transection, between the two stumps, over the lesion site, fibroblasts form a bridge, interacting with SCs [62]. The newly formed vasculature participates also in guiding the growing axons through this bridge to the distal end [63]. After a period of persistence of distal nerve stumps, distal axons disappear and dedifferentiated SCs proliferate, align, and begin emitting processes, forming the bands of Bungner (**Figure 1**), offering a physical and trophic support for the regrowth of axon [44, 60].

After the axonal regeneration, SCs differentiate once more in non-myelinating and myelinating cells to finish the functional recovery of the nerve. The regenerated myelin internodes (**Figure 5**) are shorter and thinner than the rest of the original ones in the proximal part of nerve [64].

5.2 Molecular mechanisms which control SC plasticity

The molecular mechanisms that regulate SC plasticity are very complex and widely described in many studies in recent years (reviewed in [42]). Here we will briefly mention them.

5.2.1 Transcriptional factors

One important transcriptional factor in SC reprogramming is **c-Jun**. Although it is downregulated or absent in the differentiation of SC, under pathological conditions c-Jun is particularly upregulated as described in various peripheral neuropathies [65–69], being a cross-antagonist of Krox-20 (a pro-myelinating transcription factor). c-Jun take part at the myelinophagy process [47] and participate also in the macrophage recruitment following nerve injury [70].

Another transcriptional regulator is **NICD**, an intracellular domain generated from neurogenic locus notch homolog protein (**Notch**) cleavage. SC proliferation and generation of immature SCs are controlled by Notch. But the same Notch is a negative regulator of myelination [71].

Nuclear factor kB (**NF-kB**), a transcription factor which regulates many physiological processes especially the inflammatory response, is very important for SC differentiation and myelination as *in vitro* studies showed [72–74].

In the recent years, a transcriptional repressor, **Zeb2**, has been investigated, and the researchers showed that it is implied in SC differentiation and myelination. The lack of Zeb2 in SCs results in a failure of SC maturation and in absence of myelin membranes [75].

Other factors which are overexpressed in SC dedifferentiation are **Sox-2**, paired box protein 3 (**Pax-3**), early growth response proteins 1 and 3 (**Egr-1** and **Egr-3**), and DNA-binding protein inhibitor 2 (**Id2**) [66, 76, 77]. Sox-2 is also necessary for the nerve bridge formation after nerve injury [62].

mTOR complex 1 (**mTORC1**) (reviewed in [78]) has a significant role on the transcriptome by controlling transcription factors [79–82]. It promotes anabolism, counting mRNA translation, and purine and pyrimidine synthesis [83, 84]. mTORC1 is necessary in radial sorting of axons by SCs, biosynthesis of lipids, and, on this basis, myelin growth [85, 86]. The mTORC1 activity is higher before myelination onset and decreases when myelination starts [87–89].

5.2.2 Mitogen-activated protein kinase (MAPK) family proteins

In the distal stump of the peripheral nerve after injury SCs respond by activating MAPK proteins like extracellular signal-regulated kinase (Erk), c-Jun N-terminal kinase (JNK), and p38 MAP kinase [66, 90–95].

Ras/Raf/Erk signaling in SC dedifferentiation was studied for the first time by Harrisingh et al., and they showed that the Raf activation suppresses the differentiation of primary SCs induced by cyclic adenosine monophosphate (cAMP) [91]. Raf is an activator of Erk. The authors demonstrated that the activation of Ras/Raf/Erk pathway induced demyelination in an *in vitro* study on cocultured cells—SCs and neurons from dorsal root ganglia.

Erk activation is a pro-myelinating factor, and if Erk is inhibited, the SC differentiation and myelination are blocked, showed many *in vivo* studies [96–98].

In conclusion, Erk signaling is required in differentiation (Erk low levels) but also in dedifferentiation (high Erk levels) of SCs after nerve lesion [99, 100].

JNK, another MAPK protein, is implied in SC functions, so when c-Jun is activated by JNK, the migration and proliferation of SCs are produced [19, 101, 102].

Without insisting, we would like just to remember other MAPK proteins and signaling pathways involved in SC plasticity: **p38MAPK**, **PI3K/Akt/mTOR** signaling (reviewed by [42]).

5.2.3 TLRs signaling

After nerve injury, inflammation is an important phenomenon that must be considered. Thus, Toll-like receptors (TLRs) are key factors in initiating the immune response. A number of such receptors are expressed by SCs: TLR3, TLR4, and TLR7 [103]. Some experimental studies showed an upregulation of TLRs following nerve injury, the effect being the inflammation trigger with macrophage recruitment and activation and myelin clearance via SCs [50, 104, 105].

5.2.4 Nrg1/ErbB2/3 signaling

SCs express receptors for axonal neuregulins, as it is showed in Ssection 2.2. The neuregulin/Erb2/3 signaling is strongly involved in immature SC

development but not in the regulation of adult SC proliferation after injury. An *in vivo* study on erbB2 wt/lacZ (with highly reduced ErbB2 levels in adult sciatic nerves) mice showed that after sciatic nerve transection, SC proliferation is not affected in adult ErbB2-conditional null nerves. More of this, the maintenance of myelinated peripheral nerves did not require ErbB2 function [106]. Other studies demonstrated that ErbB2 activation after sciatic nerve axotomy induced SC demyelination [107].

Neuregulin Nrg1 is still necessary for adult SC evolution after nerve injury [108, 109]. The absence of Nrg1 in adult axons results in remyelination defects after nerve crush experiments and also in a slower axon regeneration [110].

6. Therapeutical approaches based on Schwann cell plasticity

Although the peripheral nerve has a much greater regenerative capacity than the CNS nerve, the clinical recovery of patients with peripheral neuropathies is difficult, slow and often incomplete. Moreover, this capacity decreases with age.

The rate of nerve regeneration is approximately 1 mm/day, depending on the site of the lesion and on the patient age. SC plasticity diminishes with age, showing an altered expression of c-Jun [111] and a weak regenerative capacity [112, 113].

Understanding the signaling pathways that govern SC reprogramming and plasticity is essential for nerve repair and therapy.

For example, modulating Nrg1/ErbB signaling may improve myelin clearance, axonal regeneration, and finally functional nerve recovery after injury. An inappropriate overactivation of this pathway may lead to demyelinating neuropathies or tumors like neuroepithelioma and neuroplastic SC line [114, 115]. Experiments on transgenic mice with overexpression of Nrg1 showed hypertrophic neuropathies and malignant peripheral nerve sheath tumors [116]. The excessive activation of ErbB2 by *Mycobacterium leprae* determines one of the symptoms of leprosy, an important peripheral nerve demyelination [117]. In Charcot-Marie-Tooth 1A, abnormal demyelination and axon loss were prevented by Nrg1 therapy during early postnatal period in a rat model [118].

Another approach to stimulate SC regeneration and peripheral nerve functional recovery is the exogenous modulation by electric stimulation with low frequencies, photomodulation with low-level laser, and pharmacotherapy (with pharmacological agents, growth factors, bioproducts, or hormones) (reviewed by [119]).

7. Conclusions

Understanding Schwann cell biology and its extraordinary plasticity can lead to the development of new therapeutic approaches in peripheral nerve pathology and in the improvement of treatment methods in the case of traumatic nerve lesions. Peripheral neuropathies cause a significant morbidity and a decreased life quality. A better understanding of the many SC signaling pathways represents a very important approach for nerve regeneration as long as we have seen that SC is the main engine in nerve damage and repair after injury.

The recovery of the peripheral nerve, although better than that of the CNS nerve, is still quite complicated, difficult many times, and it is never perfect until the end. But in the last years, a huge amount of scientific data drew attention to the role of growth factors, transcriptional factors, inflammatory factors, hormones, and even exogenous modulation factors in the regulation of Schwann cell and of Schwann cell-axon interrelations, a complex integrated system.

It is expected that studies regarding SCs plasticity in peripheral nerve regeneration will continue and expand, improving not only the scientific knowledge but also a targeted more effective therapies, based on the pathology, personalized treatment and specific response of patients.

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Conflict of interest

The authors declare no conflict of interest.

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