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Peripheral neuro-regeneration: A narrative review of the mechanism and complications

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Abstract

Neuroplasticity differs from neuroregeneration, although both phenomena propose functional recovery after injury. The difference between both is evidenced in terms of recovery time, molecular reaction, gene and molecular expression, as well as conceptual. In this paper, we show the process of peripheral neuroregeneration and some differences between the neuroplasticity of the peripheral and central nervous system, as well as some complications of the process of neuroregeneration of the peripheral nervous system. To carry out the work, the PubMed platform was used with two batteries of descriptors to find the articles, in addition to filters that the platform provides for the selection of articles. In addition, some authors found in the platform search suggested the reading of other articles and these were included in this work according to the inclusion and exclusion methods. The process of peripheral neuroregeneration is complex, involving many signaling pathways, inflammatory and cellular response, and gene expression that favor neuroregeneration. It can be concluded that the mechanism of neuroregeneration consists of three main pillars that are pro-regenerative gene expression, inflammatory response, and Schwann cell action. However, it is not a perfect mechanism, and some complications have been evidenced.

Keywords: Neuroplasticity; Neuroregeneration; Schwann Cells; Gene Expression; Inflammatory Response; Complications

1. Introduction

After aotomy, a series of events are triggered for neuroregeneration to occur, as explained in the previous item. Genetic genetics is essential for the initiation of the process, with an ionic reaction by calcium that the axotomy itself results from. The genetic response is responsible for the response of several signals and as well as the release of cytokines, interleokines and other mechanisms of the immune response. There are signaling pathways triggered through intracellular means that are also sent to your success. The Schwann cell showed another essential part of the neuroregeneration mechanism. Genes associated with the process of myelination and non-myelination are essential for Schwann cells to undergo involution to more primitive states, triggering a positive regulation of the peripheral neuroregeneration mechanism. Furthermore, they are responsible for secreting the promotion of cell adhesion, such as control cells, which promote extracellular adhesion, such as cell cells (ECM) that promote cell attachment, such as cell cells (ECM) that promote cell adhesion. cell binding, such as cellular cells (ECM) that promote cell adhesion, such as cell control cells (ECM) It has been shown that as alterations of alterations of alterations, the alterations may change

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according to the location, suggesting the alteration of alteration of location, suggesting specificity in the neuroregeneration process. CAMs and ECMs are responsible for a number of intracellular effects and signaling that do not cause any neuroregeneration mechanism. Growth factors are also essential in the process. The variety of cellular factors, belief support and axonal growth. However, what allowed as signaling pathways for neuroregeneration are often specific to growth factors, however, as they can generate growth cone retraction and interruption of the neuroregeneration process. Changes are very important to a structure. Changes are not fundamental, as well as integrin and laminin signals are fundamental for sustaining and defining structures. The bands released by Schwann cells can stimulate growth and target corresponding targets. Schwann cells are also responsible for the myelin of the responsibility debris. The phenomenon is executed during a mechanism that functions as a mechanism that functions as a perception mechanism still necessary to be executed. However, the PMR phenomenon can be beneficial or harmful, as branches can regenerate so that they are not matched. Differences may be related and extrinsically involved in favoring or not the PMR phenomenon. In addition to the aforementioned mechanisms that favor peripheral neurogeneration, the inflammatory response is also shown to be an essential part for the mechanism to happen. In addition to all this, the possibility of creating a more favorable environment for reducing an environment to create a suitable environment for a more pleasant environment. However, nervous system like structural changes, reaction problems among others.

2. Definition

Neuroplasticity is a condition present from the birth of human life until aging. It consists of the ability of the central and peripheral nervous system to remodel itself to the conditions that are imposed, whether physiological (during development), or pathological, i.e., environmental conditions [1, 2, 4]. Conceptually neuroplasticity differs from neuroregeneration. Neuroplasticity is involved with rapid functional recovery in a short (or medium) time frame, whereas neuroregeneration consists of the ability to generate new neurons as well as new connections, providing conditions for long-term functional recovery [3].

2.1. Regeneration

The process of regeneration must be linked to the process of neurogenesis because it is associated with neuronal proliferation. Neurogenesis is the process of an increase in the integral cell cycle by the nerve cell, where the succession of phases that results in the mitosis of the mother cell, produces two daughter cells. For the neuron, this is an unusual process [1].

The precursors of neurons have a finite number of cycles and differ from regions of the encephalon. At the beginning of the cycles, division is symmetric, that is, one precursor cell will give rise to two other precursor cells and so on. This process does not last long, and at a certain point cell division becomes asymmetric. This means that the precursor daughter cell is able to cycle while the mother cell interrupts the cycle and becomes a young neuron that will migrate to its region of action undergoing a morphofunctional differentiation, a process that will stabilize this young neuron, making it a mature neuron, losing its ability to cycle1. The process of neurogenesis is identified in the dentate gyrus of the hippocampus, the subependymal zone of the telencephalon, and the hypothalamus, because there is a permanent population of stem cells in these locations that enable this process. The visual system has also been reported as a site of neurogenesis during development and its deprivation during development can lead to defective formation[1, 2, 19, 22]. The developmental capacity of axons in the central nervous system is found with the expression of a wide range of genes, such as Kruppel-like factor 7 (KLF7) and Sox11, as well as activation of the Rapamycin (mTOR) pathway, triggering intracellular signaling pathways [1, 2, 18, 21] .

Regeneration in the peripheral nervous system differs from the central nervous system. In the peripheral one can identify a true regeneration process, because the proximal stump of the sectioned axonal fiber grows to the destined site with functional reestablishment, unlike the central one that ends up inhibiting this process more than stimulating it, triggering future sequelae [1, 2, 4, 16, 18, 19].

2.2. Difference between central nervous system (CNS) and peripheral nervous system (PNS) neuroplasticity

The physiological mechanism of neuroplasticity in the central nervous system is more focused on inhibiting injured axons. Neuroinhibitory and neurotoxic molecules and structures have been identified in this process, as well as the signaling pathways that act [1,2]. When primary axon injury occurs, an inflammatory reaction is triggered in response to the first event, and is called secondary or chemical injury [1, 2, 4]. After axotomy, molecules found in the myelin of oligodendrocytes and neighboring structures are released into the extracellular environment to prevent regeneration. The molecules found are NogoA, Acrolein, Chondroitin Sulfate Proteoglycans (CSPGs), among others that act on the axon and end up inhibiting axonal growth. In addition, meningeal cells and other structures, such as gliosis, constitute

physical barriers of the central nervous system after the inflammatory reaction [1, 2, 4, 16, 18, 19]. The body tries to respond to these barriers, such as releasing the IN-1 antibody to prevent the action of NogoA, but the ratio of the antibody to the molecule is much lower, and the molecule ends up inhibiting axonal growth [1-4].

However, in the peripheral nervous system, the physiological mechanism of neuroplasticity is very favorable for the process of true regeneration. After the axotomy process, a process of cellular phenotype change occurs, resulting in the immaturation of axons and activation of genes that contribute to neuronal survival and neurite growth, and influx of calcium ions that trigger a series of events contributing to the process of neuroregeneration. The inflammatory process triggered at the site of injury stimulates the secretion of growth factors by Schwann cells (SC), and stimulates SC mitosis to potentiate this effect. Moreover, the inflammation at the site causes the macrophages found in the region to eliminate molecules that inhibit axonal regeneration, which are remnants of injured axons. The CSs have particularities that allow their survival without the need to associate with an axon, establishing an autocrine survival mechanism. If the lesions are very extensive and the loss of SCs at the lesion site is very large, nearby veins have SC precursor cells and, thus, new SCs arise to assist in the regeneration process. CSs also respond to traumatic stimuli to degenerate myelin remnants residing in the medium after injury along with the inflammatory response mediated by cytokines, chemokines, interleukins/interferons and necrosis factors, events that can be found during the process of Wallerian degeneration [1-3, 5-10, 25].

Axotomy also triggers a process of change in the phenotype of CSs that favor regeneration. Many molecules can also be localized at the site of injury (Example: Ephrin, Laminin) that promote axon growth and regeneration, some of which are not found in adult individuals, in addition to many factors that facilitate these mechanisms, for example Wallerian degeneration and neural growth factor (NGF). These events are triggered by gene expression that seeks to ensure neuronal survival as well as regeneration, as stated above. However, it is not only the genetic involvement that provides the events, but also the interaction between molecules, glia cells, growth (or neurotrophic) factors and receptors. However, it is important to note that changes in the peripheral nerves are not restricted to them, but exert influences on central nervous system structures, for example the spinal cord and thalamus. Moreover, the regeneration and neuroplasticity of the PNS are not always beneficial, and can trigger several problems for individuals, such as neuropathic pain, besides not being able to reconstruct the pathway, resulting in a defective modified pathway [2,7,10,13].

Objective

The objective of this work was to highlight basic concepts found in neuroplasticity and, from there, review the process of true regeneration after peripheral nervous system injury, highlighting the molecular components, gene transcription involved, interactions between cells and molecules, and the microstructural and cellular changes that occur for the neuroregeneration mechanism to happen.

3. Materials and Methods

The PubMed platform was used to search for the articles. Initially, two sets of descriptors were used to select the articles. The first battery has as descriptors the following words: Peripheral Nerve Injury AND Neuroplasticity AND Molecules. Without applying the filters of the search platform itself, a total of 60 articles were found. With the application of the filters - English, Human and Year 2000 until 2021 - a total of 18 articles were obtained, whose titles, abstracts and texts were analyzed for the writing of the article. Of these 18 articles, 10 articles were included. The second battery of descriptors has the following words: Molecules AND Peripheric Nervous System AND Lesion AND Mechanism. Without the application of the same filters mentioned above, a total of 103 articles were obtained. However, with the application of these filters, it was reduced to 39 articles whose titles, abstracts, and texts were also analyzed. Of these 39 articles, 16 articles were included. All the articles included were submitted to the inclusion criteria, which consisted of the platform filters and that addressed the analysis of the peripheral neuroregeneration mechanism without pharmacological and/or non-pharmacological interventions and without pre-existing diseases that interfere with the neuroregeneration mechanism. A study addressing central neuroplasticity was included in the development of the paper in order to complement the differentiation between it and peripheral neuroplasticity.

In addition to the aforementioned platform, three theoretical textbooks were used in the conformation of the article, namely: Neuroscience of Mind and Behavior 1st Edition, coordinator Roberto Lent from 2008, Rio de Janeiro - Brazil; Neuroscience 5th Edition, coordinator Purves Dale from 2012, Sunderland - USA; Wall & Melzack's Textbook of Pain 6th Edition, Koltzenburg M., McMahon S., Tracey I. and Turk D. from 2013, Philadelphia - USA, with analysis in the text by Woolf, C.J. and Salter, M. W. from 2006 entitled Plasticity and pain: role of the dorsal horn.

The authors Navarro et al (2007), Allodi et al (2012), Moran (2004) and Zigmond (2019) suggested articles to be analyzed. With this, we selected the articles they suggested and applied them to the inclusion and exclusion criteria, which resulted in the addition of 11 articles in the preparation of this paper.

4. Results and Discussion

The peripheral nervous system has a high regenerative capacity when compared to the central nervous system. Microenvironmental conditions, as well as molecule-receptor interactions, cellular events, and gene activation, contribute to effective functional recovery. However, neuroregeneration is not always beneficial and can lead to the development of complications and structural changes in the central nervous system secondary to peripheral nervous system injury [1-3, 5-8, 10-17].

It is possible to identify factors that are contributors to the regeneration mechanism. These factors are divided into intrinsic and extrinsic, and can be facilitators of the neuroregeneration mechanism and thus increase the adaptation of the nervous system, or they can promote an interruption of neuroregeneration and promote only stability. When comparing the central nervous system with the peripheral nervous system, it is possible to visualize these factors, such as the formation of the axonal growth cone (intrinsic factor) in the peripheral nervous system and the presence of gliosis, or glial scar (intrinsic factor), in the central nervous system [3, 4]. The analyses in the dorsal root ganglion, femoral and facial nerve were essential for analyses of several processes that will be mentioned and reported below, where it can be said that the events can be applied throughout the peripheral nervous system [3, 5-10, 12-17].

4.1. Ionic Reaction and Pro-Regenerative Mechanisms

Following lesion-mediated axotomy, there is an increase in neuronal calcium influx that triggers a series of events/cascades that will promote neuroregeneration. First, the process of Acute Axonal Degeneration (AAD) occurs proximal to the lesion to remove the axonal parts that were damaged by the initial mechanism of injury [3]. In the axonal part distal to the lesion, the active degeneration mechanism called Wallerian Degeneration occurs and is initiated by the suppression of the rapidly degrading Nicotinamide Mononucleotide Adenylyltransferase 2 (NMNAT2) regulated by sterile alpha and TIR motif containing 1 (SARM1). This type of degeneration is evidenced 24 hours after injury and lasts for 1 to 2 weeks, where it is possible to identify axon necrosis and phagocytosis of other axonal debris mediated by macrophages (main phagocytic cells found at the site), transported by the blood, and by Schwann cells, eliminating inhibitory factors of neuroregeneration present at the site that are associated to myelin, the main one being glycoprotein [3, 8, 10]. Thus, Wallerian Degeneration provides a suitable and favorable site for axonal growth [3, 7, 8, 9, 10, 19].

Calcium is also responsible for other changes that occur early in peripheral nervous system injury. Initially Calcium causes axonal sealing and formation of the retraction bulb to occur, and in the later part, the ion promotes activation of calpains, responsible for the degradation of the submembranous cortex of spectrin. This degradation is necessary because it allows the access of vesicles at the axonal end that carry new receptors and membrane components. Calcium also provides the activation of Mitogen-activated Protein Kinase Kinase kinase dlk-1 (MapKKK dlk-1), resulting in the formation of the growth cone [3, 18].

After the mentioned degenerations, Schwann cells (SCs) organize and are stimulated to form Büngner bands, known as long chains aligned in strands in the basal lamina tubes that fill the inter-fragmentary spaces and thus form guidance channels for axons that will regenerate to their respective target organs, synthesizing many neurotropic and neurotrophic molecules to aid regeneration. The CSs that form the bands are known as repair CSs and have the ability to proliferate (2-3x more compared to mature CSs) and elongate (7-10x more compared to mature CSs), contributing to this formation. Axon sprouting starts in the end bulb about 3 hours post injury. Initial axonal sprouting and are short-range projections guided by local cues and actin-rich filopodia are responsible for recognizing these cues consisting of neurotrophic and/or adhesion factors. Individual filopodia also alter internal Calcium concentrations upon stimulation of the microenvironment and in the parts of the growth cone, they respond by metabolizing actin [3, 9, 10].

The growth cone needs to be sustained to ensure future regeneration. Because of this, a large amount of proteins are synthesized for this support to occur effectively, as well as for axonal maintenance, repair and regeneration. These events are successful due to the presence of 3,000 messenger RNAs (mRNAs) and other cellular structures, such as ribosomes and Golgi complex-like components, present in axons. Calcium is responsible for activating the transcription of importins and the Ran binding protein (RanBP) which, through retrograde mechanisms of action, are responsible for the uptake of Vimentin and Erk (Erk1 and Erk 2), being transported to the nucleus and resulting in regeneration-associated gene expression (RAGs). Another signal for regeneration includes the N-terminal c-jun kinase (JNK). However, the growth cone is already formed before the synthesized axonal proteins reach the lesion site. Many other

transcription factors have been described and reported to be of paramount importance for growth and functional recovery through regeneration and include c-Jun, JunD, Fos, and translocation of ATF3 to the nucleus, culminating in formation of complexes with DNA-binding activity. Other transcription factors described as important for growth/regeneration are STAT, P311, Sox11 and C/EBPb, positively regulated after injury and activated, as well as proteins (GAP-43, CAP-42, Sprr1a, among others) [3, 10, 18, 21, 23, 24, 32, 46, 47].

Other events attributed to Calcium can also be observed. Through the protein kinase Cmu (PKCμ) pathway, histone deacetylase 5 (HDAC5) is displaced in the nucleus-cytoplasmic direction, allowing gene translocation, previously suppressed, through acetylation of histones that ends up positively regulating the synthesis of RAG-associated transcription factors, such as for example c-jun and c-fos. In addition, HDAC5 is transported to the growth cone where it will promote axonal growth by deacetylation of microtubules. The positive regulation of RAGs triggered by calcium ion ends up promoting axonal priming (or conditioning effect), which will culminate in a more accelerated regenerative process in future lesions [3, 18, 21].

4.2. Growth Cone and Microstructural Changes

The growth cone is formed due to a transformation of a stable axonal segment into a mobile end. As mentioned earlier, the Schwann cells form so-called Büngner bands, and through these the growth cone is able to proceed to its final destination. However, it is not only an axonal sprout that is generated after injury. Each axon in the regenerative process ends up generating more than 10 axon sprouts, but in the distal segment, the number of branches decreases with time due to the atrophy process because they do not make peripheral connections. Nevertheless, after a long time from the beginning of the lesion, the neurons that are in the regeneration process are able to sustain several axonal sprouts that branch from the level of the lesion in the distal nerve stump, thus explaining the larger amount of nerve fibers in the distal stump when compared to the actual number of proximal fibers that regenerate after the lesion [5, 7, 46]. The main cytoskeletal structures capable of promoting axon elongation are actin, myosin, and microtubules [10]. In addition, the microstructural changes found are essential for growth cone advancement, and will be elucidated in the following paragraphs [7, 10].

Growth cone advancement is guided and guided by neurotrophic and neurotropic factors that are mainly produced by non-neuronal cells. Chemotaxis is provided by interaction between the distal nerve stump and these factors, which can be chemo-attractive or chemo-repulsive, and can also be diffusible or membrane-bound [3, 7].

The aforementioned growth cone progression can be observed thanks to three initial stages: 1) Protrusion; 2) Ingurgitation; 3) Consolidation. In addition, it is possible to identify three specific functional regions that contribute to the initial stages. The regions are named as follows: 1) Central Domain (CD); 2) Transition Zone (TZ); 3) Peripheral Domain (PD). The regions are interconnected and the microstructural changes, as well as the composition of each, contributes to the early developmental stages cited [7].

The DC is composed of microtubules, while the PD is composed of actin and the ZT is found between these two domains. Due to actin polymerization, the growth cone membrane undergoes a protrusion, contributing to the delivery of new microtubules to the PD, as well as stabilizing it along the actin bundles. With this, the DC engorgement occurs, that is, the displacement of the DC forward, in addition to promoting the consolidation of the nascent axon. The concentration of components in a certain region can lead to microstructural changes for the positive regulation of the growth cone. Such an effect can be seen in the formation of the actin filament arch, a process triggered by the high concentration of soluble tubulin at the distal end of the microtubules of the DC, and by the high concentrations of myosin in the ZT, promoting actin contraction. In addition, it is worth mentioning the microstructural characteristics that are found in the PD. In the distal portion of the growth cone, in which this domain is found, it is possible to identify membranous protrusions called lamellipodia, from which come out expansions called filopodia, which are formed by actin filaments, giving the growth cone a shape similar to a "winged foot". The filopodia act as "tentacles", whose function is to explore the surrounding microenvironment. This exploration is possible thanks to the establishment of an equilibrium force between the polymerization and depolymerization of actin, thus generating constant protrusion forces [7, 10].

In the consolidation phase, protein alterations of the cytoskeleton are found. The proteins in regenerating axons undergo changes equivalent to those found during axon development. These changes can be evidenced by an increase in the concentration of tubulin, actin, and peripherin isoforms and a decrease in the concentration of neurofilaments that are responsible for regulating axon caliber. These changes are observed after transection of motor and sensory fibers. Due to the regenerative process, the metabolic demand is very high, causing an increase in the synthesis of several components in the neuronal body, being transported in an anterograde manner to the end of the fiber, besides protein

synthesis and degradation in the axon. Because of the protein changes, as well as their synthesis and degradation, which may be associated with microtubules and actin, new microtubules are assembled in the DC [7].

For the mechanism of growth cone advancement to be adequate, the intracellular medium must be stabilized. Microtubule formation in the growth cone is related to calcium influx, cyclic nucleotides, post-translationally modified tubulin, and microtubule-associated proteins (MAPs). As the growth cone advances and microtubules are incorporated into the cytoskeleton, modified tubulin enhances microtubule stability, causing depolymerization to decrease [7].

The stability of microtubules in the cytoskeleton is also related to two classes of structural proteins, which can be called MAP (MAP1-MAP5) and the tau proteins, MAP5 being important in the reorganization of the cytoskeleton. The two favor the mechanism of tubulin polymerization and remain bound to the newly formed microtubules. Besides this mechanism, MAPs promote cross-links between microtubules and cellular components and are also highly phosphorylated, serving as substrates for phosphorylating enzymes and GAPs, especially GAP-43, which is found with very increased levels in peripheral nerves in regeneration process, being phosphorylated via PKC, activating PLC-Ɣ through the TrkA receptor pathway [7, 14, 24].

Proteins fundamental for the neuroregenerative process can also be found in the cytoskeleton. GTPases belonging to the Rho family, are upstream signaling pathways for downstream cytoskeletal rearrangement in a very specific manner that reproduce changes from the extracellular environment into the cytoplasmic environment and are recruited by receptor complexes found in the growth cone itself to control, also, actin-myosin mediated contractility [7]. However, not only GTPases play an important role in neuroregeneration, but other molecules also play an important role in this process. Rho-associated kinases (ROCKs), as well as other Rho family molecules and their effectors, are important in the mechanism of neuroregulation, having a complex system of activation and regulation, and different guidance cues in the extracellular environment activate different GTPases. At the same time, other trophic molecules and laminin, an extracellular matrix molecule, can interact in a coordinated manner in the same GTPase to regulate neurite growth [7, 24]. Laminin also interacts with integrins and by combining, they play an essential role for the mechanism of neuroregeneration [7, 9]. Study involving axotomy of the facial nerve, evidenced that a process of synaptic removal occurs, a reversible phenomenon after the reinnervation process. However, after complete axotomy, it is possible that the astrocytic isolation of motoneurons is long-lasting, functioning as a functional glial scar [14].

4.3. Molecule-receptor-cell interaction and its effects

For the mechanism of neuroregeneration to proceed, it is essential that molecules interact with cell receptors to trigger the cellular effect expected for axonal regeneration [3, 5, 7-10]. Experimental studies have been analyzed and have become essential for the elucidation of signaling mechanisms for proper cone (or neurite) growth formation and growth to occur [7, 9]. With this, understanding about neurotrophic factors, adhesion molecules, extracellular matrix molecules, among others, is necessary, remembering that it is not the focus of the article to detail the interactions of each of them.

4.3.1. Laminins, Integrins and their effects

The interaction between laminin and integrin are important for the regeneration mechanism and interact with molecules of the extracellular matrix and basal membrane (Examples: Laminin, Collagen and Fibronectin) [7, 9]. Conceptually integrins can be defined as glycosylated heterodimers that are formed by α and β subunits. Furthermore, they are understood as type I transmembrane proteins with non-covalent associations that have one cytoplasmic (β) and one extracellular (α) component. It has been identified 18 α and 8 β subunits, and their possible combinations can form 24 different integrin complexes and can be grouped into different subfamilies according to function/interaction [7].

The signaling of integrins are understood as follows: "inside → outside" and "outside → inside" and have simultaneous chemical and mechanical functions. They are also responsible for controlling the Rho protein as well as the translocation of Rac1 and Cdc42 to the plasma membrane [7, 24].

A relationship between sensory neurons and integrins has been established. It has been suggested that the expression level of these receptors in adults are reduced compared to neonatal cells, causing the number of neurites to be lower in adult cells, which hinders the regenerative process. However, it was observed that in addition to the variability of alpha subunits of cells within the dorsal root ganglion (α1, α3, α5 , α6 and α7), forced expression of integrin α1 culminated in a growth of adult sensory neurons almost equivalent to the developing ones found in neonates. The receptor for integrin α9, when overexpressed, is capable of promoting axonal regeneration in mature sensory neurons. The dorsal root ganglia have been shown to be important for studying the regenerative mechanism [7, 9].

Laminins fall into the family of heterotrimeric glycoproteins, being located in the basal lamina, and have several specific isoforms. Approximately, 11 laminin chains form 15 heterotrimers different from each other in a variety of tissues, where each has the α, β, and γ subunits, with a cross rearrangement, being named from laminin-1 to laminin-15 [9]. However, 45 different combinations of the laminin subunits with tissue-specific localization have already been identified[7]. Laminins have also been shown to be essential in the mechanism of peripheral regeneration [7, 9].

Despite their varied functions, one can highlight cell growth/migration, tissue regeneration and cell differentiation/adhesion, as observed in Schwann cells that express laminins and stimulate axonal growth as well as cell differentiation and myelination, and interfere with inhibitory signaling of myelin-associated glycoprotein. This phenomenon was best observed with the expression of α1β1γ1 (laminin-1) which promoted the growth of all developing neuronal classes, suggesting that laminins function as axonal guidance molecules [9].

Furthermore, laminin-1 has been shown to be effective in redirecting axons to their correct place. The inhibitory site of laminin-1, when interacting with a factor secreted by dorsal root ganglion axons, caused repulsion, evidencing a role in the mechanism of reinnervation, and also, the different isoforms of laminin may be related to this mechanism. Laminin-2 (α2β1γ1) is also found abundantly in the peripheral nervous system and is also able to promote neuroregeneration like laminin-1 [9]. In addition to these laminins, other types have also been reported to be critical for neuroregeneration. The α4β1γ1 (laminin-8) and α5β1γ1 (laminin-10) have also been described as fundamental to the regeneration mechanism. The corresponding integrin receptors for laminins-2, -8 and -10, are α1β1, α2β1, α6β1, α7β1 and the sidecans [7].

After nerve injury, a peak of laminin-8 levels was observed in the first 3 days post-injury and normalized in the subsequent 42 days, proving to be a key part of this type in the initial regeneration process, as well as laminin-2, with the increase of the latter lasting longer than 42 days [7]. Initially, temporary coordinated expressions of laminin α4 and integrin α6 subunits occur, indicating a relationship with Schwann Cell proliferation. Later, expression of laminin α2 and integrin α7 occurs, with a function more directed toward axons for regeneration [7]. It has been stipulated that motoneurons have a preference for laminin α2 substrates, while sensory ones lean toward laminin α4. However, there is still not enough data to prove this theory, as well as not having a differential pattern in the expression of both isoforms [7]. At the same time that this situation is occurring, integrin receptors are positively regulated after peripheral nervous system injury and are very important for the mechanism of neuroregeneration, such as the expression of laminin-associated integrins α6β1 and α7β1 [23]. As already reported, neuroregeneration studies of dorsal root ganglia have proven effective in understanding the mechanisms, and have also highlighted an extensive and complex signaling network for growth [7, 9].

4.3.2. Components of the Endoneural Extracellular Matrix (ECM)

ECM components are produced by Schwann cells and fibroblasts. Studies point out that ECM molecules have both stimulatory and inhibitory molecules for axonal growth [7, 8, 9]. The inhibitory stimuli are the predominant factors in the adult neuron to prevent the emergence of collateral fibers, however, in the event of an injury, a process of reversal occurs and the stimulatory mechanisms are activated so that the neuroregenerative mechanisms occur. The components of the ECM are capable of promoting interactions between receptors and cell adhesion molecules, besides containing some molecular types capable of stimulating the neuroregenerative process. In addition, the amount of molecules synthesized by Schwann cells in efferent and motor axons are different, leading to quantitative and qualitative molecular variations. One can state that these findings suggest a specificity when it comes to the targeting of the final targets of peripheral neuroregeneration [5, 7, 9].

Didactically, the components of the ECM can be divided into two major groups which are: Proteoglycans and Glycoproteins. The glycoprotein group can be further subdivided as follows: Collagen and Non-collagenous molecules. Laminins have been described previously and are part of the ECM, and are also very important for stimulating axonal growth [7, 9]. The components of the ECM are mentioned and listed below.

Chondroitin Sulfate Proteoglycans (CSPG)

They are found in the endoneurium of peripheral nerves (Example: Versican CSPG and Decorin) in a widespread manner and are related to the mechanisms of support and inhibition of axonal growth by interacting with laminin, interfering in the signaling of integrins [7, 9]. In an intact and mature peripheral nerve, the inhibitory activity of CSPGs is recognized by the monoclonal antibody CS-56, and this recognition is more expressive in the distal stump of the peripheral nerve after injury [6, 9]. This proves to us that CSPG co-localizes with laminin within the basal laminae of Schwann cells, inferring that it has a very wide distribution within the endoneural tubes in the degenerating nerve [9].

Fibronectin (FN)

A glycoprotein formed by blocks of three types of homologous repeated peptide sequences. Many homologous blocks form functional domains organized in a linear array on two subunit arms. The specific domains of FN support the mechanisms of cell-cell adhesion and cell-basal membrane attachment, and also very significantly promote peripheral axon growth and Schwann cell migration [7, 9]. In addition to being secreted by Schwann cells, FN interacts with collagen IV and laminins to trigger the mechanisms of cell proliferation and differentiation. It is also able to bind to integrins and other molecular types, such as heparin and syndecan [7].

Tenaskines (TN)

Glycoprotein with restricted and dynamic expression, widely found during the development and regeneration of the nervous system. They are substrate-bound and soluble, producing effects that differ greatly in axonal growth, and at one point may exhibit adhesive and soon after anti-adhesive properties. Such activities are controlled by different domains of the molecule [7, 9].

Thrombospondins (TSP)

A glycoprotein that is expressed throughout the developing nervous system, promoting axonal growth and has been proven to have such an effect in in vitro and in vivo studies [9].

Glycosaminoglycans (GAGs)

These molecules are enhancers of neuritogenesis, in addition to promoting nerve regeneration and muscle reinnervation, and should hold in interaction with insulin-like growth factor-1 (IGF-1) [7].

Collagen

These are trimeric molecules formed by 3 α-chains, and are divided into subfamilies according to the type of structures they form. Collagens have been found to have important functions in axonal localization and connection/maintenance of synapses [7, 11].

4.3.3. Cell Adhesion Molecules (CAM)

CAMs are responsible for promoting interactions between molecules found on the ECM and cell surfaces [7, 12]. Cadherins and integrins mediate these interactions [7]. To understand the integrins, we recommend seeing the topic 4.3.1. The analysis of CAMs, mainly L1, Neurofascin, Axonin-1 and F11, were compared with laminin, where it was evidenced that, with the exception of F11, all the others were able to promote the growth of neurites, being the most expressive in elongation L1 and Neurofascin. However, the combination of L1-Neurofascin was the best for the neurite growth process, while L1-Axonin-1 and Neurofascin-Axonin-1 were not efficient, and the latter combination even inhibited the growth mechanism [12]. The studies involving the femoral nerve was crucial for understanding the action of these molecules, especially L1 and neural CAMs (NCAMs), which are able to promote neurite growth. The homolog of L1 (CHL1) has also been shown to be important for the mechanism of motoneuron regeneration [5, 7, 12-17, 48].

Cadherins promote cell adhesion and consist of a superfamily of immunoglobulins (IgSF) with approximately 50 different members. The best known and studied is the N-cadherin that has an important and essential role in axonal growth/fasciculation and synaptic formation/consolidation [12]. Regarding the diversity of immunoglobulins (Ig), one can highlight neural CAMs (NCAMs) that promote neurite growth through FGFR phosphorylation and Fyn association. A specific form of NCAM (polysialylated) is essential in the regeneration of motor nerve branches and in the positive regulation of preferential reinnervation of muscles. Polysialic acid (PSA) interacts with NCAM and is highly related to the development of the nervous system. The amount of PSA is differentially expressed in motoneurons and sensory neurons, indicating a selectivity at the time of regeneration. PSA also increased the process of motor neuritogenesis by expression of low molecular weight fibroblast growth factor 2 (FGF-2). The PSA-NCAM combination interacted with FGFR-1, an FGF-2 receptor, hypothesizing that FGF-2 favors the interaction between FGFR-1 and Schwann cells and PSA-NCAM in motoneurons. However, the NCAM-FGFR interaction promoted the proliferation of Schwann cells as well as the remyelination process of regenerated axons. Recently, histone H1 has been shown as a novel ligand of PES, promoting neurite length in neurons and the process length and proliferation of Schwann cells [5, 7, 10-17]. For an in-depth look at IgSFs and their effects, it is recommended to review the authors Irintchev, A., & Schachner, M. and their 2012 study [17]. Many other molecules are also reported to be important for the mechanism of neuroregeneration. Klimaschewski and colleagues [10] in 2013, revealed that comprehensive reviews have described other molecular types that are associated with neuroregeneration and are somewhat important for its mechanisms, such as galanin and pituitary adenylate cyclase (PACAP).

Other CAMs are also able to promote Schwann cell proliferation and positively regulate the phenotypic memory of these cells, which is the case of the interaction of the L2 molecule and HNK-1, an interaction that can be found in motor Schwann cells, and also that the HNK-1 molecule can promote motor axon regeneration [5, 7]. Other assignments of NCAM and HNK-1 can be found in Schwann cells, and we recommend seeing topic 4.4.

4.3.4. Growth Factors and Cytokines

Neurotrophic factors are widely known to be essential for neuronal survival during the period of post-injury development. Non-neuronal cells synthesize and secrete several factors in order to maintain homeostasis in uninjured neurons. However, after injury, an expressive increase in these factors occurs in an attempt to promote axonal survival/growth that are in the process of regeneration and reinnervation in their respective target organs [5, 7, 10, 13, 14, 29, 30, 31]. Neurotrophic factors can be divided into the following groups: 1- Neurotrophins; 2- Glia-derived Neurotrophic Factor; 3- Fibroblast Growth Factor; 4- Insulin-like Growth Factor; 5- Neuregulins; 6- Pleiotrophin (PTN); 7- Osteopontin; 8- Neuroactive Cytokines. It has also been shown that neurotrophic factors are also expressed differently in motoneurons and in sensory neurons, favoring preferential motor reinnervation (PMR). Other factors, such as hepatocyte growth factor (HGF), vascular endothelial growth factor-1 (VEGF-1), insulin-like growth factor 1 and 2 (IGF-1; IGF-2) and fibroblast growth factor (FGF-2), are found after axotomy and will also be mentioned below. Differentiation factor 5 (GDF-5), is currently classified as a growth factor although it belongs to the protein subfamily, and is associated with survival of dopaminergic neurons and the astroglial cells found in the dorsal root ganglion (DRG) [5, 7, 10, 13-17, 29, 30, 31].

Regarding Schwann cells, there is a difference in the expression and concentration of growth factors in the dorsal and ventral roots and in cutaneous and motor peripheral nerves. Under normal conditions, Schwann cells in the dorsal root express IGF-1 and BDNF, while in the ventral root, PTN and IGF-1 are expressed. Upon causing a lesion, the concentrations change. In the dorsal root an increase in BDNF, GDNF, HGF and NGF occurs, while in the ventral root the expression of PTN and GDNF increases. In cutaneous nerves, under normal conditions, Schwann cells express NT-3, HGF, BDNF and FGF-2, while in motor branches, there is expression of PTN, IGF-1 and BDNF. After an injury in cutaneous branches, there is increased expression of HGF, NGF, VEGF, BDNF and IGF-1, while an injury in motor branches there is increased expression of PTN and IGF-2 [5, 7]. In addition, myelination regulators, both positive (Example: Krox-20) and negative (Example: c-Jun), are activated after axotomy and growth factors, as well as interleukins, are important for myelination expression and sorting. These regulators are important for the many intracellular signaling pathways that will trigger axonal regeneration and functional recovery after injury [20-23, 29, 30].

Neurotrophins and their receptors

They are represented by nerve growth factor (NGF), brain-derived growth factor (BDNF), and the neurotrophins 3 and 4/5 (NT-3; NT-4/5). The neurotrophins respond to specific receptors called tyrosine kinase (Trks), with the three subtypes being called TrkA, TrkB and the TrkC. The TrkA receptor is of high affinity for NGF, acting on primary sensory neurons, especially small ones, while Trk B is of high affinity for BNDF and NT-4/5 being found on medium-sized spinal and primary sensory motoneurons. In addition, Trk B has two subtypes called TrkB.T1 and TrkB.T2. The former is much more prevalent and expressed in adult brain nerve cells and its expression is greatly increased in adult glial cells after axotomy and it is believed that it may be involved in neural maturation and response to nerve injury. TrkB.T2 is little known, but is speculated to have the same effects as TrkB.T1. TrkC is a high-affinity receptor for NT-3 and is found on large diameter primary sensory neurons. A low-affinity receptor for neurotrophins called p75NTR is also found, however its role is controversial as it also promotes pro-apoptotic responses by modulating part of the Rho family [5-7, 10, 13-17, 29, 30, 31, 35, 48].

When the axotomy process occurs, TrkB and TrkC receptor levels are reduced in Schwann cells of the injured distal nerve, whereas these reduced levels are reported in DRG neurons in the soma for the TrkA receptor, but an increase occurred in the regenerating nerve. Transport of neurotrophins in sensory neurons responds to p75NTR and Trk receptors, but only P75 is expressed in motoneurons. Neurotrophins and the neutrophin-receptor signaling mechanism trigger changes in the growth cone and enable axonal growth [5, 7, 10, 13, 14, 17, 29, 30, 31].

NGF is important for the collateral appearance of nociceptive and sympathetic axons in denervated skin and has no function on large sensory neurons. Application of NGF soon after axotomy, delays the onset of regeneration by reducing the response in the neuronal body, but does not prevent further regeneration. BDNF is expressed differently in motor and sensory nerves, and after injury, it is more expressed in cutaneous nerves compared to ventral roots. The role of BDNF is still controversial, but by binding on the TrkB receptor, it is able to sustain nerve regeneration. BNDF is also important for axonal growth, myelination and nerve regeneration in neural conduits. NT-3, under normal conditions, is found in cutaneous sensory nerves than in motor nerves, however, its concentration changes after injury, however, it

can also be localized in the trigeminal, cervical and lumbar spinal ganglia. NT-3 is present in adult skeletal muscles and has trophic action on motoneurons (selective action on fast muscle fibers type 2b) and on primary sensory neurons that innervate the muscles, besides having an important function in the survival of proprioceptive and mechanoceptive sensory neurons. NT-4 was able to promote functional reinnervation of slow motor units.Recently the neuroprotective factor of cholecystokinin-8 (CCK-8) , an important signaling agent in the CNS and PNS, has also been suggested. Its effect seems to be to counteract neuronal deficit in chemical or surgical injury by stimulating NGF synthesis [5, 7, 10, 13-17, 29, 30, 31, 34, 35, 47].

Glia-derived Neurotrophic Factor (GDNF)

GDNF belongs to the TGFa-1 superfamily, and exerts a trophic effect on sensory, motor and autonomic neurons. Non-peptidergic neurons of small diameter lose their sensitivity to NGF and become sensitive to GDNF. Despite its concentration in the peripheral sensory branches, after axotomy, there is a marked increase in GDNF concentrations in the ventral and dorsal roots after injury, and it is released by Schwann cells, promoting regeneration at these sites and is more effective than NGF. Increased expression of GDNF provides adequate long-term regeneration and promotes increased numbers of motoneurons in chronically injured nerves, being able to regenerate their axons, and promotes the injury effect of conditioning at low concentrations. The positive regulation of GDNF, provides positive regulation of its receptor, GFRa-1. Upon binding with the receptor, recruitment of Ret occurs which ultimately phosphorylates Ret-specific tyrosine residues, culminating in intracellular signaling, which will result in the positive regulation of regeneration. However, other receptors named GRFa-2, GFRa-3 and GFRa-4 have been identified, which are specific for neurturin, persephin and arteminin. After axotomy, GFRa-1 and Ret are increased in large diameter neurons in the DRG, GFRa-3 is increased in small diameter ones, and a reduction in GRFa-2 occurs after injury. Other glia-derived neurotrophic factors are also widely found after peripheral nervous system injury and are able to favor regeneration, called Neurturin (NTN), Persephin (PSP), and Artemin (ART) [5, 7, 10, 13-17, 29, 30, 46].

Fibroblast growth factor

FGF-2 has been shown to be an important factor in nerve regeneration. It is important to remember that FGF-1 is also framed as an important factor in the process of neuroregeneration. The isoforms of FGF-2 are regulated differently during development and after injury. After axotomy, FGF-2 is expressed in neurons, increasing the number of regenerating axons after injury by increasing Schwann cell proliferation, and increasing axon and myelin size. The receptors for FGF-2 are FGFR 1-3 which are positively regulated after the injury process, and after activation of extracellular signals regulated by kinase (Erk) and Akt pathways, trigger an overexpression of FGFR-1. FGF has been found to maintain interactions with heparin and heparan sulfate proteoglycan (HSPG), increasing the affinity of the FGF-FGFR complex [5, 7, 10, 13, 14, 29, 30].

Insulin-like growth factor

Its representatives are IGF-1 and IGF-2 with endogenous regulatory functions in the repair and regeneration processes, as well as assisting in the development of motoneurons and in survival after the axotomy process. Under normal conditions, i.e. without axotomy, IGF-1 is expressed in ventral and dorsal roots and muscle branches, whereas after injury, IGF-1 expression is increased in cutaneous branches, while IGF-2 is increased in muscle branches. However, studies suggest that IGF-1 induces neurite outgrowth in sensory neurons through signaling of the PI3-kinase pathway, and also increases the speed of the regeneration process, significantly improving functional recovery. It has also been evidenced that IGF-1 promotes motor branch regeneration mediated by increased motoneuron sprouting. In addition to IGF-1 and IGF-2, IGF binding proteins (IGFBP) 4 and 5 show expressive increases after nerve injury, while IGFBP-6 mRNA increases in post-injury spinal motoneurons. It has been reported that IGF-1 is decreased with life span and that its endogenous application favors axonal regenerative mechanism and muscle reinnervation in aged animals [5, 7, 10, 13, 14, 29, 30].

Neuregulins

In this class, one can highlight neu differentiation factor (NDF), Heregulin, acetylcholine receptor inducing activity (ARIA) and glial growth factor (GGF). The first two can be found in growth and differentiation mechanisms of breast epithelial cells, while the latter two are widely found in the neuromuscular junction and Schwann cells during development, and GGF is expressed in sensory, motor and sympathetic neurons as well. Specific receptors named erbB2, erbB3 and erbB4 have been reported to exert effects on Schwann cells and are important for the interactions between these cells and neurons. After axotomy, there is an increase in GGF mRNA synthesis and an increase in erbB2 and erbB3 receptors in the distal nerve stump. GGF is able to promote proliferation and maturation of Schwann cells, as well as their migration to and decrease of myelin debris. ErbB receptor signaling has also been shown to be effective in the process of Schwann cell differentiation and myelination, as well as the establishment of neuromuscular junctions and

development of normal sensory function by interacting with neurogulin 1. The importance of neurogulins are evident and exert important roles and functions in Schwann cells, cell-cell interactions and in the process of Wallerian degeneration itself by autocrine and paracrine signaling [5-7, 10, 13, 14, 30].

Pleiotrophins (PTN)

This is a protein secreted by binding to heparin. It is expressed in the nervous system during its development and promotes postsynaptic clustering of acetylcholine receptors. Under normal conditions, PTN is expressed in the ventral root and muscle branches and, after injury, its expression is increased and positively regulated in these same sites, evidencing a preference profile. Furthermore, its expression is increased during the first two days, reaching a maximum peak after 7 days, returning to basal levels after 3 months. PTN was able to promote neurite elongation of motoneurons and axonal regeneration, but was not able to promote their survival, and results pointed out that its application in peripheral nerves in vivo was detrimental for muscle reinnervation [5, 7, 10, 13, 14, 17].

Osteopontin

This is a matricellular glycoprotein that is widely expressed by macrophages after central nervous system injury and has not been found in the peripheral nervous system. What is known about this molecule is that it is expressed by myelinating Schwann cells in uninjured peripheral nerves and that after axotomy, an increase in this expression occurs in the distal nerve stump, with a negative up-regulation after 14 days [5, 7, 10, 13, 14]. More recent studies, evidenced that osteopontin is able to promote neuroregeneration in the optic nerve and other sites of the visual system [18, 21].

Neuroactive cytokines

Many cytokines can be cited in this item and are widely found after axotomy due to the gene expression that occurs. Ciliary neurotrophic factor (CTNF) is produced by Schwann cells and found in uninjured peripheral nerves. After the axotomy process, overexpression of CTNF in Schwann cells triggers an increase in myelin protein expression and activates their differentiation. CTNF is also able to bind to the a-ret receptor on neurons promoting a paracrine effect related to cell and motoneuron survival, as well as promoting axonal growth and able to assist the guidance of reinnervation and axon sprouting in motoneurons. CTNF expression was equal in cutaneous and motor branches under normal conditions and after axotomy. Another factor that uses the same signaling pathway as CTNF is leukemia inhibitory factor (LIF). Schwann cells produce LIF and it is retrogradely transported by the subpopulation of small diameter neurons in the DRG, most of which are positive for IB4 and the rest for TrkA and CGRP. Axotomy triggers positive regulation of LIF and is responsible for promoting regeneration of motor pathways and sympathetic and sensory neurons, as well as their survival. Interleukins also play a role in regeneration. Interleukin-6 is positively regulated after injury, and its receptors are able to promote regeneration. IL-6 has also been shown to have an effect on conditioning injury. There is controversy about the role of IL-6 in the axonal growth conditioning injury, where authors argue that it is sufficient but not necessary. The mRNA expression of IL-6 and its receptor in Schwann cells is greatly increased in the presence of FGF-2, playing a key role in the regeneration process [5-7, 10, 13-21, 23].

4.4. Schwann cells

Axotomy not only triggers the effects mentioned above, but other cellular events are encountered and triggered by the initial injury. Schwann cells (SCs) are affected and stimulated by the initial injury to promote neuroregeneration of the peripheral nervous system. When they lose axonal connections due to the lesion, they return to stage II development, which corresponds to their immature state. In this state, a cascade of events is triggered for future recovery. First, SCs must be differentiated as myelinating or non-myelinating. This classification can be adopted because of the positive (Example: Krox-20, Oct-6) and negative (Example: c-Jun, Sox-2) regulators of myelination that trigger intracellular signals in Schwann cells that will exert their respective functions. In stage II, after the loss of axonal contact, some specific markers can be found, such as cell adhesion molecule L1, neural cell adhesion molecule (NCAM) and mouse neural antigen 2 (Ran-2). However, the main markers found that will differentiate SCs into myelinating and non-myelinating are as follows: NCAM and the Natural Carbohydrate Killer-1 (HNK-1), conferring molecular identity in SCs. Reconstruction of the lost circuitry of motor axons is accomplished by myelinating SCs that have expressed L2/HNK-1. In addition to this specific marker, other markers can be found, for example protein 0 (P0), Conexin 32 and Galactocerobroside (Gal-C). However, it is not enough just to myelinate the fibers, but a finer tuning of this process is necessary, being controlled by axonal signals, the main one being called Neuregulin 1 (NGR1) type III. In contrast, SCs that are not myelinating expressed NCAM and had negative regulation of L2/HNK-1 in non-autonomic sensory fibers associated with cutaneous branches. Other markers are also found in the nonmyelination process, such as glial fibrillary acidic protein (GFAP) and growth-associated binding protein 43 (GAP-43). GAP-43 is also closely related to the mechanisms of neuroregeneration, and is found at different sites in the nervous system as a whole. It can be noted that the molecules mentioned belong to different families, but they play roles on Schwann cells and in regeneration

mechanisms. For example, NCAM belongs to the immunoglobulin superfamily (IgSF), as do L1 and CHL1 and are important for the pro-regenerative mechanism. These molecules have also been shown to influence central nervous system mechanisms and interact with distinct receptors, for example neuroprotective effects reported following NCAM-FGFR interaction in spinal cord injury [3, 7, 9, 13-17]. Schwann cells are also responsible for secreting molecules that will be found in the ECM, which are critical for axonal growth and regeneration. Gene expression is able to positively and negatively regulate for myelination and immature and/or denervated Schwann cell states and have been extensively reviewed [7, 9, 10, 13-24].

One attribution of gene expression is evident in Schwann cells. Expression patterns vary in motor and sensory branches. Some genes were found in motor branches that mediate myelination and signaling, such as filament light polypeptide (Nefl) and protein kinase C iota (Prkci), while in sensory branches, neuroligin (Nlgn1) and myelin basic protein (Mbp) were expressed, as well as other genes that promote proliferation and migration, for example nap1l1, dok4, lpp, mmp-9 and l1cam [3, 5, 9, 10].

4.5. Inflammatory Response

As previously mentioned, the inflammatory response plays a fundamental role in peripheral neuroregeneration, but not always acting in favor of the best functional prognosis of the patient. Two agents gain prominence in the process of injury and regeneration, they are the SC and macrophages. These two cell types are essential in the clearance and phagocytosis of myelin debris and glycoproteins associated with myelin (MAG) at the injured site. These debris inhibit regeneration and render susceptible still intact cells in the case of a partial nerve injury, the latter being potential targets for complement [6,19, 22, 25, 48]. A few moments after axotomy, the SCs and resident macrophages are the first to react to the injury, releasing chemokines and cytokines such as IL-1, CCL-2 and LIF, causing the first biochemical changes at the injury site and promoting the chemical attraction of circulating macrophages [8,19]. The SCs near the axons react to axotomy by releasing TNF alpha, IL-alpha and IL-1beta from 5 to 10 hours after injury, that is, before the arrival of hematopoietic Macrophages [19, 25]. The first peak of SC activity lasts until approximately 5 days after injury, during Wallerian degeneration and then, in a second moment, their action returns to occur in regeneration. After the first two days of injury circulating macrophages enter the axotomized region by CCL2 stimulation. In mice in which the genes for CCL2 or for its receptor CCR2 were deleted, macrophage infiltration and response to injury does not occur in DRG [6]. As for the role of macrophages, it is suggested that it is mediated by complement receptor 3 (CR3) in the context of trauma. Furthermore, the degenerated myelin itself activates the production of the complement protein C3bi, which promotes a twofold increase in phagocytosis by expanding the binding sites of CR3, whereby they become C3bi opsonized myelin and non-opsonized myelin [19]. It is known that there are two distinct populations: pro-inflammatory macrophages (M1) and anti-inflammatory macrophages (M2), however there is no consensus about which populations act more in which phases, it is believed that M1 predominates in Wallerian degeneration while M2 is present in the regenerative context. Still on Macrophages, their function extends beyond phagocytosis, in the vicinity of the cell body they promote a conditioning response to injury, a process in which neurons increase their proliferation after a previous injury [6, 22, 25]. The function of SC and Macrophages in peripheral regeneration appears to be essential and interrelated. Although immunity has positive regulation in peripheral neuroregeneration, it can also be assessed as deleterious in certain instances. An example of this is the expression of CD47 by SC, reducing myelin phagocytosis and hindering regeneration, since it is correlated to the speed and intensity of myelin depletion at the axotomy site [19]. The immune system and the inflammatory response play a crucial role in peripheral neuroregeneration, and further elucidation is needed in order to better understand its agents.

4.6. Gene Expression

Throughout the work, it is possible to identify that gene expression is involved in several processes of neuroregeneration, being a main pillar in the mechanism. As for example, the ionic reaction provoked by calcium that promotes the displacement of HDAC5 reported in section 4.1. More comprehensive reviews on the vast gene expression, as well as other types of studies, are needed to better elucidate the gene pathways activated during the regenerative process. The most recent studies have corroborated and elucidated even more about the mechanisms of nervous system development evidencing intracellular signaling pathways, promoting organization capacity and synaptic and morphological neuroplasticity evidenced at the beginning of the article [1, 2, 18, 21, 22].

Gene transcription, in addition to what has already been mentioned, is involved with the mechanisms of myelination, activation of signaling pathways (such as MAPK, PIK / Akt, SMAD, PLC-g, Erk and others), promotion of the release of growth factors/cytokines and inflammatory response through activation of interleukins and pro and anti inflammation factors. The activation of these mechanisms for neuroregeneration is crucial for functional recovery after injury [8, 13, 18, 21-24, 32].

Understanding the genetic mechanisms involved has been used as a bridge to better elucidate the key factors for peripheral neuroregeneration. The role of genetics extends from the most direct, such as the expression of RNAms for NGF production, to the as yet little known abnormal expression of microRNAs (miRNA) in peripheral nerve lesions. Transcription factors such as STAT3 and SOX 11 are found in regulatory function and expressed after injury. Modification in these factors triggers hyper expression of genes related to the repair mechanism. Mature neurons utilize the translation of axonal RNAms to send injury signals to the nucleus as a form of signaling, through retrograde signals essential for the initiation of the regeneration process [3, 23, 46, 47]. Despite this, not all RNAms behave the same way upon injury, NGF RNAms are expressed longer in shear injuries, suggesting that neurons that regenerate in crush injuries have their NGF expression reduced [19]. The expression of genes, proteins and mediators of injury and repair are dependent on the period in which the process is located, after axotomy of the sciatic nerve the expression of CCL2 and its corresponding RNAms was observed at the injury site, while later in the distal portion of the segmented nerve. The reprogramming of SCs upon injury is a result of the action of the transcription factor c-Jun, important for phenotypic changes in the SC that propitiate regeneration. When c-Jun is inactivated in mouse SCs they become less favorable to repair [20, 22, 23, 48]. Another relevant factor is miRNA 21, induced after in vivo axotomy of the DRG, which promotes regeneration through its overexpression. Moreover, the loss of viable neurons is an obstacle in the functional recovery of nerves, so genes that hinder or prevent apoptosis deserve to be mentioned. In DRG the gene GADD45A is positively regulated and protects cells from damage, preventing cell death [22, 25]. The interaction of genetics in the process of peripheral neuroregeneration is vast and interconnected, with not only the genes involved being regulators but their RNAms and proteins produced, dependent on the environment of the lesion.

4.7. Complications Encountered

The process of peripheral neuroregeneration comes with its own potential complications, as previously mentioned. Among them, it is worth mentioning neuropathic pain, but it is not the only one, and it is reported the presentation of allodynia, hyperalgesia, dysesthesia and phantom pain, or phantom limb syndrome [1, 2, 8, 33]. Alteration in the pattern of function and expression of ion channels, such as calcium and sodium channels (Navs 1.1, 1.2 and Navs 1.6-1.9), are potential contributors to genesis and maintenance of neuropathic pain after injury because they promote electrophysiological modifications, not only at the axotomized site but in neighboring uninjured fibers [8, 27, 36, 37, 41-45]. Furthermore, they have their altered expression and function generating ectopic firing, contributing to sensations of hyperalgesia and allodynia, the latter being related to the interaction of up-regulation of the α2δ subunit of the calcium channel, with neurokinin-1 receptors, p38 MAPK, P2X4 and neuronal c-jun deletion, also contributing to neuropathic pain and hyperalgesia. High calcium influx also provides activation of hydrolytic enzymes, high energy expenditure and defective energy production, causing cell death and is associated with behavioral and cognitive deficits, and may be implicated with defective neuronal regeneration. Structural rearrangement is also associated with the development of aberrant neuronal circuits, among other changes and dysfunctions arising from structural rearrangement, and other genes, such as β2-microglobulin (TAP1), and molecules, such as MHC I, may contribute to nociceptive reactions and impaired peripheral neuroregeneration. In addition, structural rearrangement alters the expression of AMPA, NMDA and GABAergic receptors also have a role in the mechanism of neuropathic pain, where there is a decrease in GABAergic receptors and an increase in AMPA and NMDA expression at the synaptic membrane through activation of several pathways, such as PKC, PKA and CMAK2 cascades [3, 8, 16, 27, 36-45].

Regarding genetic mechanisms, the Fxyd2 gene expression plays a role in controlling the activity of the α1-catalytic subunit of Na-K-ATPase in non-peptidergic nociceptors, playing a role in inflammatory pain and its chronification [28]. Furthermore, the JAK/STAT signaling pathway induced in the spinal cord in response to peripheral injury in rats is one of the initial stages preceding the development of allodynia [26, 27, 28]. In cases where there is complete nerve transection and discontinuity of tissue without the possibility of elongation towards the distal nerve a neuroma may form, associated with dysesthesia and pain [7, 8]. Peripheral regeneration results in incompatibility of neural connections promoting loss or decrease in tactile and discriminative acuity, as well as the onset of painful symptoms. Injuries can also trigger low activation of Schwann cells and end up preventing new connections with muscles, that may trigger atrophies and other problems, besides the activation of the calcitonin gene (CGRP) that impairs neuroregeneration and recruitment of Schwann cells. Other mechanisms affecting myelin differentiation are linked to peripheral neuropathy mechanisms, and these mechanisms are known as negative regulators of myelin and are: c-Jun, Notch, Sox-2, Pax-3, ld2, Krox-24, and Egr-3. As mentioned earlier, suppression of c-Jun leads to a considerable delay in the initial degradation of the myelin sheath, in the inactivation of myelin genes, and possibly to impaired action of factors such as L1, p75NTR and N-cadherin. The transmembrane receptor Notch also promotes demyelination in the myelin sheath. Sox-2 inhibits the activation of myelin genes and shows elevation after nerve injury. Pax-3 can suppress induction by c-AMP or Krox-20, without suppressing L1 or NCAM, markers of immaturity, but its role in the adult remains to be studied. The researchers hypothesized that Id2 may be related to both myelination antagonization and Schwann cell dedifferentiation. The roles of Krox-24 and Egr-3, are still poorly defined and further studies are needed

to establish their roles. Other agents that may be related to myelinating cell dedifferentiation are ERK1/2, Neuregulin-1, Neurotrophin 3 (NT3), Purinergic signaling and Nitric Oxide synthase [7, 8, 13, 48].

A study involving axotomy of the facial nerve, evidenced that a process of synaptic removal occurs, a reversible phenomenon after the reinnervation process. However, after complete axotomy, it is possible that the astrocytic isolation of motoneurons is long-lasting, functioning as a functional glial scar. The central deafferentation mentioned has been proven in humans after electro-functional studies, in addition to data on the negative regulation of PSD-95, a protein involved synaptic plasticity and synaptogenesis. This suggests a central alteration after peripheral nerve axotomy [14].

The increased expression of NT-3 and BDNF, increasing its activity in sensory neurons, translates into an enhanced regeneration capacity after PNS nerve injury. Therefore, in animals with this reduced activity they may show a weaker global regenerative feedback to axotomy. Moreover, marked neuronal death culminated in increased muscle reflex responses, and other clinical evidence has shown that nociceptive stimuli are capable of sensitizing central structures and also contribute to hyperreflexia, hyperalgesia or persistence of pain [8, 30].

PMR has been described in several studies in mammals as a preference of motor neurons to regenerate toward muscle fibers over skin tissue. The most widely used models to study this phenomenon were femoral nerves from rats and mice, and it can be observed that such an event is dependent on the conditions of the study, the time factor, the size of the nerve fiber, and the signaling of the target organ. Polysialic Acid seems to trigger PMR in some motoneurons of the quadriceps femoris, just as the application of antibodies against MAG accelerates the preferential motor innervation after femoral nerve injury in mice. The cited effect opens the question about the origin of the pathway preference, and further elucidation is needed to understand its mechanisms and implications for peripheral neuroregeneration [5, 7, 8, 17].

5. Conclusion

The mechanism of peripheral neuroregeneration is complex and involves detailed steps for the process. We can state that the mechanism consists of three essential pillars that are necessary for its initiation, these being gene transcription, Schwann cell activation, and the inflammatory response. With these three pillars, the following steps of the mechanism of reconstruction of the lost pathway flow in an orderly manner. However, some gaps still need to be filled to avoid the complications of peripheral neuroregeneration. The phenomenon of preferential motor reinnervation must be better studied and elucidated. The imbalance of these three pillars (Gene Transcription, Schwann Cells, Inflammatory Response) is correlated with chronic neuralgia and allodynia or paresthesia mechanisms as a result of synapse asynchronism, aberrant number of axons formed after injury, central axonal remodeling, among others. The inflammatory mechanism also has great relevance in this process, because the synaptic remodeling and the lesion that the inflammation itself causes in adjacent neurons may be linked to the activation of nociceptive pathways, causing a varied chronic pain mechanism, and the direct link between neuropathic pain secondary to peripheral lesion can already be proven. In view of these issues, it can be speculated that peripheral neuroplasticity may become maladaptive over time, whereby through chronic synaptic remodeling, associated with an imbalance of the preferential motor reinnervation phenomenon and aberrant numbers of end axons, results in a noncompensatory and harmful mechanism for patients. Studies and further experiments should be conducted to work on this hypothesis in the long term.

Authors' opinion

We consider that the mechanism of peripheral neuroregeneration is important for maintaining the interaction between environment and the central nervous system. However, the mechanism should be considered maladaptive or compensatory depending on the final outcome. Peripheral neuroregeneration happens in order for the interaction between the nervous system and the external environment to happen, however certain complications make it undesirable and we can extend this reflection to the central nervous system. The mechanism of inhibition of neuroregeneration of the central nervous system can be seen as a protective mechanism for it, considering that the mechanism can be more harmful than beneficial to the patient, that is, the central nervous system considers that the risk of neuroregeneration is more harmful than the benefit that the mechanism can offer, this being an evolutionary remnant of natural selection. From this reflection, one can consider the following question: Individuals who do not possess the ability to regenerate the central nervous system were positively selected for the perpetuation of the species in comparison with those who possessed this capacity, not being a malefic characteristic, but an evolutionary remnant necessary for the perpetuation of the species.

However, it is worthwhile to think and consider another aspect. In the evolutionary aspect, the nervous system was peripheral to maintain interaction with the external environment. However, the improvement of the nervous system occurred over the years, and the central nervous system developed with greater potential in mammals and primates, beings involved until this evolutionary phenomenon. In view of this evolution over the years, some questions can be raised: The fact that the nervous system regenerates itself, was it not an evolutionary adaptation, which occurred before in these species?, or, moreover, is it a matter of time for that the regenerative phenomenon happens in humans, which can still be considered an involuted species in this regard?

There are many questions that time and natural selection will answer.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare that they have no conflicts of interest in writing and publishing the article.

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