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REVIEWS

Current Views on Schwann Cells: Development, Plasticity, Functions

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Abstract—The review addresses current concepts on the origin and functions of Schwann cells (SCs) as well as phenotypic characterization of their precursors at different ontogenetic stages. The necessity of versatile fundamental exploring SCs is dictated by searching for novel ways to stimulate the recovery of peripheral nerve fibers, including cell and gene therapy. Being a major structural component of the nerve, SCs have a decisive influence on degenerative and reparative processes therein. Particularly accentuated is the lack of knowledge of the molecular mechanisms that regulate SCs differentiation at different ontogenetic stages and their plasticity in the pathology of nerve conduction.

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INTRODUCTION

The topicality of studying morphofunctional features of Schwann cells (SCs) can be explained two reasons. First, it is impossible to overrate the general biological significance of these myelin producers and the very process of myelination for the development of the nervous system. Second, profound knowledge of the developmental patterns and mechanisms of SC functioning is crucial for developing the means to stimulate regeneration of damaged nerve conductors.

The importance of SCs for the myelination of nerve fibers is due to the great evolutionary significance of the emergence of myelin in the course of evolution [1]. With its advent, synchronization of muscle contractions was simplified, the nervous system became more compact, and there appeared the possibility for complex information to be processed faster [2, 3]. Salzer and Zalc [4] consider axonal myelination as an adaptive response that emerged during evolution to promote the development of faster nerve conduction.

One of the major functions of SCs is isolating neighboring nerve fibers.

The second reason that determines the importance of tackling SCs is the necessity of understanding molecular and cellular mechanisms underlying regeneration of damaged nerves. A host of works, both domestic and worldwide, address the structure and regeneration of peripheral nerve conductors. Such studies were initiated in the XIX century by a British neurophysiologist August Waller (1816—1870) [5]. A complex of neural posttraumatic processes that occur at the distal end of the nerve trunk was called by his

name, Wallerian degeneration. Later on, many researchers used neuromorphological, histochemical, immunohistochemical and electron microscopic approaches to investigate cell–cell interactions in a damaged nerve. In classical neuromorphological studies it was shown that basic structural components involved in degenerative and reparative processes in a damaged nerve are motor, vegetative and sensory neurons whose processes make up a peripheral nerve, as well as SCs, macrophages, vascular cells, and connective tissue elements that ensheath a nerve [5–8].

A special interest in studying the molecular mechanisms of regular and posttraumatic interrelationships between structural components of peripheral nerves has appeared in the last decades due to the development of gene and cell technologies which can promote regeneration of peripheral nerve conductors after their injury [9–16]. The urgency of such studies is due to the fact that the methods being applied in the microsurgical practice to treat nerve damages not always lead to their complete functional recovery. One of the reasons behind these mishaps is an insufficient knowledge of fundamental molecular mechanisms of nerve regeneration. Also, it is not clear which mechanisms underlie the influence of cell transplants (including genetically modified cells with overexpression of growth factors) on reparative processes in a damaged nerve.

In view of a great evolutionary significance of SCs and their importance for regeneration of damaged nerves, it appears reasonable to summarize and generalize the currently available data on the origin of these cells, their morphofunctional features, development and differentiation. This was the aim of the present review.

SCHWANN CELLS: MYELINATING AND NONMYELINATING

In the middle of the XIX century, Theodor Schwann, a German physiologist, described the cells wrapped around axons of the peripheral nervous system (PNS) [17]. These cells were called after his name [18]. Notably, there is yet another term to define SCs as “lemmocytes” which was coined by Nils Ragnar Eugene Antoni (1887–1968), a Swedish neuropathologist who studied tumors deriving from the peripheral nerve sheath [19]. In the Ramon y Cajal’s works, glial elements described in a damaged nerve were called both Schwann cells and lemmoblasts [6]. The terms lemmocytes and lemmoblasts are being also used now by some authors [8, 20]. In the opinion of Nozdrachev and Chumasova [8], lemmoblasts represent one of the developmental stages of SCs which are distinguished form their earlier precursors by the ability to form a basal lamina. It is noteworthy that in the current domestic histological nomenclature there is one more synonym of SCs, a neurolemmocyte [21].

SCs can be divided into two groups, myelinating and nonmyelinating cells. Both of them play a key role in maintaining axonal trophic and regenerative processes in the PNS. Most of peripheral nerve conductors in vertebrates are myelinated. Nonmyelinated are small-caliber axons. Notably, in the CNS, where the role of myelinating cells is played by oligodendrocytes, axons of some neurons remain nonmyelinated, e.g., slender axons of cerebellar granule cells which ascend to the molecular layer of the cerebellar cortex and ramify therein [22].

The question of which group SCs refer to, myelinating or nonmyelinating, is resolved during embryogenesis at the stage of immature SCs [23]. Currently, many signaling pathways regulating the development of SCs and the process of myelination are well studied [1]. It is generally believed that the question of whether or not an axon will be myelinated depends on the type of the axon adjacent to precursor cells, as well as on its molecular microsurrounding (the presence of extracellular matrix proteins, mainly of laminin). A central role is attributed to type III neuregulin 1 (NGR1-III) that regulates axonal pathfinding. Large-caliber axons produce a high level of NRG1-III which promotes differentiation of precursor cells into myelinating SCs, and one cell myelinates one fiber. Small-caliber axons are characterized by a low level of NRG1-II secretion which results in differentiation of precursor cells towards nonmyelinating SCs [23–26]. At the same time, NRG1-III is essential for differentiation both of myelinating and nonmyelinating SCs [27]. Thus, in addition to the signaling pathways already studied, it is still to be found out which

Table 1. Characterization of Schwann cells at different stages of differentiation

Differentiation stage	Characteristics	Markers	Ref.
Schwann cell precursor (SCP)	Like neural crest cells, able to migrate and proliferate. The viability relies on signals from growing axons. SCPs migrate together with growing axons. Regulated by neuregulin 1 (NRG1). NRG1-mediated activation of ErbB2/3 is important both for SCP proliferation and targeted migration.	Sox10, GAP43, Oct6, Sox2, MPZ	[23, 27, 37]
Immature Schwann cell (iSC)	Derive from SCP and cease to migrate. Form the basal lamina. Survival of iSC does not depend of axonal factors. During iSC differentiation in nerves, blood vessels and fibroblasts begin to form; collagen appears in the extracellular matrix. The perineural sheath arises. Regulatory mechanisms of this differentiation stage are understudied; the involvement of Notch signaling is suggested.	Sox10, S100, GAP43, P75NTR, NCAM, Sox2, Oct6, MPZ GFAP, O4	[23, 27, 37]
Pro-myelin Schwann cell (pro-mSC)	Arise at the stage when a 1 SC/1 axon ratio has been achieved and all the large-caliber axons have been separated. Pro-mSC form their own basal lamina. Those iSCs, which wrap the remaining small-caliber axons, differentiate into Remak SCs.	Sox10, S100, Krox20, Oct6	[27, 37]
Non-myelinating Schwann cell (nmSC)	nmSCs wrap small sensory and vegetative PNS axons, thus forming a classical Remak bundle. Retain their proliferative potential. Terminal SCs. SCs in Pacinian and Meissner's corpuscles.	Sox10, S100, GAP43, P75NTR, NCAM, Oct6 Egr-1, GFAP and AN2 / NG2	[27, 28, 37]
Myelinating Schwann cell (mSC)	Form myelin sheathes in nerve fibers of most nerves.	Sox10, S100, Krox20, Oct6, MBP, MPZ P0/Pmp22/ MAG/MBR	[18, 37]

other external signals control the development of SCs and myelination. It is unknown if there are some negative signals which prevent myelination of nonmyelinated nerve fibers [27]. It also yet to be ascertained what influence not only axonal signals but also other cell types (endothelial cells, fibroblasts) exert on differentiation of SCs during ontogenesis [27].

Nonmyelinating SCs have some distinctive morphological features which distinguish them from myelinating cells. First, they align along axons at a smaller distance from each other; second, they tend to contact more than one axon [27, 28]. Such cells enclose several slender (less 1 μm in diameter) axons without forming a myelin sheath and make up a structure called a Remak bundle. In the PNS, there are several classes of nonmyelinated nerve fibers: nociceptive C fibers, postganglionic sympathetic and parasympathetic fibers, and motor nerve terminals in neuromuscular synapses [27, 29]. Nonmyelinating SCs comprise the sensory Pacinian and Meissner's corpuscles [29]. Nonmyelinating SCs associated with small-caliber axons are called Remak SCs [30]. In innervating the skin, when Remak bundles approach the epidermis, their SCs attain a ratio of one SC per one axon. Subsequently, these fibers lose a contact with SCs, and only axons alone enter the epidermis. In contrast to myelinated axons, these fibers are characterized by a continuous growth which is under control of the nerve growth factor secreted by nonmyelinating SCs [30].

Nonmyelinating SCs associated with axons in neuromuscular synapses are called terminal or presynaptic SCs [31, 32]. Whether terminal SCs perform a trophic function towards axons, as Remak SCs do, is unknown. Presumably, they are involved in synaptogenesis during development, as well as in reinnervation of nerve fibers after injury [27, 33, 34].

THE ORIGIN OF SCHWANN CELLS IN EMBRYOGENESIS

In embryogenesis, SCs originate from the neural crest, an anlage which forms during a closure of the neural tube and resides in the form of strands on both sides of it. Migrating multipotent cells of the neural crest give origin not only to SCs but also peripheral neurons, melanocytes, neuroendocrine cells etc. [see reviews: 18, 25, 23, 35, 36].

After migration, neural crest cells pass through several stages of differentiation towards SCs: SC precursors (SCPs), immature SCs (iSCs), nonmyelinating SCs (pro-mSCs), and ultimately differentiated SCs among which some are myelinating while others are nonmyelinating (mSCs and nmSCs) [23, 25]. The developmental dynamics of SCs and their phenotype is presented in Table 1.

SC precursors are distinguished from neural crest cells by being already in close contact with axons. There are some data that they are multipotent cells able to differentiate not only into SCs but also to endoneural fibroblasts and some other cell types [23, 25]. When describing these cells, the authors draw a parallel with radial glial cells in the developing CNS which, being neural stem cells, are multipotent and give rise to neurons, astrocytes, ependymal cells and oligodendrocytes. The molecular mechanism of neural crest cell differentiation into SC precursor cells is poorly studied. There is only some evidence that this process involves Notch signaling [23]. An interesting feature of SC precursor cells has also been described: they die in the absence of axons.

Phenotypic characteristics of SCs differ depending on the ontogenetic stage. SC markers at different developmental stages are studied both *in vivo* and *in vitro*. Liu et al. [37] analyzed specific markers of cultured SCs in neonate mice using immunofluorescence, Western blotting, and quantitative real-time polymerase chain reaction. They revealed ten markers specific to SCs *in vivo*: S100, p75NTR, Sox10, Sox2, GAP43, NCAM, Krox20, Oct6, MBP, and MPZ. At all stages, there were only detected transcription factors Sox10 and Sox2. After 8 days of culturing, all markers showed up except GAP43 and Oct6. The widely used markers S100 and P75NTR were found not to be expressed at the early stage of SC culturing.

The mechanisms underlying differentiation of immature SCs into nonmyelinated cells are poorly explored. There is evidence that this process recruits laminin, an extracellular matrix protein. On the strain of mutant mouse devoid of laminin, Yu et al. [27, 28] showed that it is exactly this protein that is required for stimulation of SC differentiation.

Immature SCs (iSCs) perform important histogenetic functions. First, they isolate large-caliber axons (that will eventually become myelinated) from small-caliber nonmyelinated fibers. Second, they produce trophic factors that stimulate differentiation of such structural nerve components as perineural cells, vascular cells, endo- and epineural fibroblasts [27].

FUNCTIONS OF SCHWANN CELLS AND THEIR PRECURSORS

Myelination of peripheral nerve fibers

Two mechanisms evolved to increase the speed of nerve impulse conductance. The first is concerned with an increase in the axon diameter, while the second relies on the emergence of the myelin sheath [38]. Myelination enabled the conductance speed of small-caliber axons to be increased. Myelinated nerve fibers are inherent to most vertebrates. Phylogenetically, they emerge in cartilaginous fishes. In sharks, skates and rays it shares basically the same organization as in all other vertebrates: nerve fibers are enclosed by the basal lamina, surrounded by collagen, and have numerous Schmidt–Lanterman incisures and nodes of Ranvier. It was established that like in other vertebrates, myelin sheathes in cartilaginous fishes contain myeloproteins PO, MPZ and the myelin basic protein (MBP) [39].

As for invertebrates, different types of myelin were described in members of various taxa. Ones have dense myelin sheathes, whereas others exhibit naked neurites wrapped by several glial cell membranes [38, 40]. For instance, in some crustaceans (crabs, lobsters), mollusks and insects, myelin sheathes are not described as yet, and the function of isolation is performed by nonmyelinating glial cells and elements of connective tissue. In those crustaceans which have myelin sheathes, e.g., plankton copepods, myelin shares similar organization with that in vertebrates [41]: it is characterized by concentrically arranged membrane layers which envelope the axon. The number of layers per sheath varies in different axons from 1 to 50 and more. Highly organized myelin layers are tightly swirled around the axon crammed with microtubules. The sheath consists of electron-dense same-thickness layers which alternate with thicker and less dense ones [41]. Such an organization of myelin in vertebrates and invertebrates owes to the identical function of myelinating cells.

The question of which environmental conditions led to the emergence of myelin in invertebrates still finds no clear explanation [38]. Presumably, a high speed of nerve impulse conductance is vitally important for those animals which have to gather high speed when fleeing from a predator or, vice versa, pursuing a prey [4, 38]. This assumption is supported by the fact that the population range of copepods that have myelinated nerve fibers is far wider compared to that of their same-subclass counterparts lacking myelinated axons. Still debatable is the question of where myelin and myelinating cells had first emerged during phylogenesis: in the central or peripheral nervous systems [42]. Some authors believe that PNS SCs and CNS oligodendroglia share a common precursor in evolution [2]. However, there is a lot of difference between these cell types. For instance, they have different origin in embryogenesis: oligodendrocytes derive from the neuroectoderm while SCs from the neural crest. There are also numerous distinctions between the processes of myelination that proceed along the central or peripheral types. They are regulated by different transcription cascades: Sox10, Olig1/2, and MYRF for oligodendroglia and Sox10, Pou3F1, and Egr2 for SCs. In addition, it is well known that in the CNS and PNS myelinating cells exhibit different myelin packing mechanisms. Supposedly, myelin structures emerged in the CNS and PNS in parallel. It is also assumed that myelin emerged several times during evolution [4]. There is paleontological evidence that the first vertebrates that had myelinated nerve fibers were shellfishes (Testacea) [2, 3, 38].

The molecular regulatory mechanisms that underlie myelination of peripheral nerve conductors are being actively studied now on various models. Among them are in vitro culturing of neurons and SCs, transgenic animal and nerve injury models, etc. [43].

It is generally believed that the thickness of the myelin sheath depends on the diameter of a nerve fiber [8, 22]. During the formation of the myelin sheath with a certain thickness a key role is played by NRG signaling through ErbB receptors [43–45]. NRG signaling is essential for SCs to express structural components of the plasma membrane and to create a requisite number of myelin wraps around the axon. It was demonstrated on transgenic animal models that in the absence of NRG-III myelination does not occur [18]. The importance of NRG for myelination is proved by the fact that normally nonmyelinated processes of sympathetic neurons become myelinated under in vitro conditions if these neurons overexpress NRG [24].

Trophic function of Schwann cells

The fact that myelinating cells (oligodendrocytes or SCs) perform a trophic function towards a nerve cell and its axon has been previously noted by many authors [1, 8, 22, 46], and now state-of-the-art research methods have only provided further proof that glial cells, both in the CNS and PNS, influence axonal metabolism. For instance, it has been demonstrated that oligodendrocytes synthesize lactate that prevents axons from degeneration [47]. It has also been established that impaired function of mitochondria in SCs entails progressive degeneration of myelinated axons [48]. An important role in axonal metabolism is also ascribed to nonmyelinating SCs [27, 48].

Studies of the relationship between SCs and axons have shown that they can exchange their

organelles. There is evidence that ribosomes can be transferred from SCs to axons during development [1]. Experiments that demonstrate the transfer of polyribosomes from SCs to axons were carried out with the aid of GFP both on in vitro and in vivo models, with GFP specifically tagging SC ribosomes. After penetration into the axon, ribosomes were observed therein for several weeks, being likely involved in local protein synthesis [49]. There is an opinion that in the region of the Schmidt–Lanterman incisures and nodes of Ranvier there may occur a transfer of RNA from SCs to axons [50].

Trophic function of glial cells can be of particular importance for the PNS because peripheral nerves reach a considerable length and transport of metabolites, as compared to that of vesicles, is slow (300 μm/h) [4].

Exchange of genetic information between Schwann cell and axon via a release of exosomes

Exosomes and microvesicles are extracellular nanovesicles released by many cells [51]. They mediate cell–cell interactions via a transfer of genetic information, including that of both coding and non-coding RNAs, to recipient cells. Exosomes reach a size of 10–100 nm. It was shown that they can transfer fragments of matrix RNA (mRNA) and microRNA (miRNA) from cell to cell [15, 51]. In studying SC–axon interactions, many authors have demonstrated that exosomes released from SCs influence regeneration of injured axons. The reviews [50, 52] provide versatile characterization of exosomes and mechanisms of their formation, as well as their importance for axon–glia relationships.

In model in vitro experiments, it was shown that exosomes of SCs uptaken by axons of peripheral nerves stimulate growth of neurites [52]. This effect was found to be specific for exosomes obtained exactly from SCs, as proved by the fact that exosomes synthesized not in SCs but in fibroblasts have no such an influence. The stimulatory effect of SC exosomes on axonal growth was also confirmed in in vivo experiments. It was shown that daily injections of exosomes into the distal segment of an injured nerve lead to double the axon growth rate.

Exosomes are assumed to be involved in the regulation of Wallerian degeneration [50]. They are known to be able to modulate the cell phenotype through transfer of mRNAs, miRNAs and protein transcription factors in various organs [51]. This suggests that during differentiation exosomes can mediate switching the definitive myelinating phenotype of SCs to nonmyelinating.

Synthesis of biologically active substances

SCs influence nerve cells by producing neurotrophic factors, cytokines and extracellular matrix proteins. It was established that they exert a supportive effect on developing neurons until their axons have not yet reached target organs [44]. For instance, in ErbB3-deficient transgenic mice (i.e. in the absence of SC precursors) spinal motor neurons and sensory neurons located in the spinal ganglia die through apoptosis [44].

After traumatizing a peripheral nerve conductor and injuring an axon, SCs exert a supportive effect on neurons synthesizing a number of biologically active substances, such as the nerve growth factor (NGF), fibroblast growth factor (FGF), brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF), glia-derived neurotrophic factor (GDNF), neurotrophin 4/5, neurotrophin-3 (NT-3), ciliary neurotrophic factor, neural cell adhesion molecule (NCAM) and others [15, 53–56]. The evidence for the necessity of these factors for maintaining neuronal viability and differentiation was obtained on transgenic animal models. Defective synthesis of these biologically active substances can lead to neurological diseases and abnormal nerve regeneration.

As is well known, nerve injury entails dedifferentiation of SCs. Dedifferentiated SCs acquire the capacity of synthesizing some proteins of the extracellular matrix (laminin, fibronectin, tenascin etc.) which participate in the stimulation of axonal regeneration [15, 27, 55]. They also secrete chemokines and cytokines required for the recruitment of monocytes/macrophages to a nerve. Among them, they are MCP-1 (monocyte chemoattractant protein-1), LIF (leukemia inhibitory factor), PAP-III (pancreatitis-associated protein III), and interleukins IL-1α and IL-1β [57–59].

SCs are able to synthesize substances that are

involved in the regulation of nerve morphogenesis. First, they produce a protein which controls the formation of the perineurium, DHH (desert hedgehog) [60]. The perineurium is one of the sheathes of the nerve stem sheathes which provides the perineural barrier protecting the endoneurium from exogenous infectious agents. Second, SC precursors associated during embryogenesis with certain nerves can secrete the vascular endothelial growth factor A (VEGF-A), thus promoting vasculo- and angiogenesis in the developing nerve [61].

Thus, due to the ability to produce some biologically active substances, SCs provide trophic support to developing neurons until their axons have not yet reached their targets, maintain the viability of nerve cells and the posttraumatic integrity of the nerve trunk, and also participate in morphogenesis.

Involvement in phagocytosis of myelin breakdown products during Wallerian degeneration

Wallerian degeneration unfolds in the distal segment of an injured nerve trunk and includes a breakdown of the axon and its myelin sheath. Although it is thought to appear mainly due to a mechanical trauma of nerve trunks, it was also described in toxic and metabolic lesions of nerves [62]. Degeneration of the nerve fiber's axial cylinder leads to disrupt its connection with the myelin sheath and causes myelin breakdown. To ensure normal regeneration of nerve fibers, it is necessary to clear a nerve from axonal and myelin breakdown products. The question of which cells are involved in the removal of myelin breakdown products has long been considered debatable [8, 62]. The role of phagocytes that remove myelin degradation products in an injured nerve was attributed not only to macrophages but also to SCs. It was generally believed that SCs of myelinated fibers get rid of myelin upon injury and that part of them participates in phagocytosis of its breakdown products. This was proved by electron microscopic studies which showed that after nerve injury the cytoplasm of SCs abounds in myelin-derived lamellar structures. However, there is also evidence that rules out the involvement of SCs in this process. For instance, on the model of nerve fragment survival in a diffusion chamber it was established that under conditions of nerve isolation from exogenous monocytes/macrophages myelin phagocytosis does not occur [63]. Later on, many authors proved the crucial role of monocytes/macrophages in the removal of axonal and myelin breakdown products in injured nerve conductors [22, 64, 65].

The development of immunohistochemical techniques for identification of SCs and macrophages allowed establishing that both cell types are involved in the removal of myelin degradation products [62]. Currently, there is no doubt that during the first days after nerve trauma the function of clearing myelin debris at the distal end of the nerve is fulfilled by SCs, whereas the final purge of the endoneurium requires the recruitment of macrophages [22, 62, 66]. In current studies, the mechanism of eliminating myelin breakdown products by SCs is being revised. Specifically, there is an opinion that this mechanism cannot represent phagocytosis since phagocytes engulf only what is outside of them, while the myelin sheath is an integral component of SCs, their part. In this connection, it is hypothesized that the mechanism of engulfing myelin breakdown products by SCs is macroautophagy [67, 68]. Macroautophagy represents a degradation system in which cells lyse their own organelles and large macromolecules. Gomez-Sanchez et al. [67] showed that after traumatizing the nerve trunk it exhibits activation of SC autophagy which manifests itself in the formation of autophagosomes containing myelin debris. While observing autophagy of the SC myelin sheath, the authors termed this process “myelinophagy”. It was demonstrated on experimental models that genetic and pharmacological inhibition of autophagy inhibits degradation of myelin proteins and lipids in an injured nerve.

PLASTICITY OF SCHWANN CELLS

Phenotypic plasticity of SCs manifests itself when SC–axon interactions become disrupted due to traumatic injury. This disruption leads to dedifferentiation both of myelinating and nonmyelinating SCs into immature forms.

After nerve injury, mature SCs receive a signal from the injured axon through the NRG/Erg2

system and change their phenotype [22]. It was shown that Erg2 is activated during the first several minutes after nerve trauma, and over the following two days after losing contact with the axon SCs dedifferentiate [22]. Dedifferentiated cells are able to migrate and proliferate. Due to their division, they form in the distal segment of the traumatized nerve the so-called Büngner bands which represent axon regeneration pathways. In addition, they begin to synthesize anti-inflammatory cytokines and chemokines that stimulate macrophage infiltration [59, 69]. When contact with the axon is restored due to regeneration, these cells become again myelinating or nonmyelinationg, depending on signals emitted by the regenerating axon [18]. Regulation of dedifferentiation and proliferation of SCs, as well as following remyelination of regenerating axons recruits extracellular matrix proteins, neurotrophic factors and hormones [55]. Dedifferentiated SCs (i.e. cells that form the Büngner bands at the distal end of the traumatized nerve) acquire the properties of immature SCs [70]. Recently, it has been demonstrated that they also exhibit specific traits that distinguish them from other cells in the SC lineage. Gomez-Sanchez et al. [71] have shown that injury of the mouse sciatic nerve leads to alter both the structure and function of SCs. The cells assume an elongated shape and form processes. It was also shown that Büngner band cells are 2–3 times longer than myelinating and Remak SCs and 7–10 times larger than immature forms [71]. Notably, when these cells transform again into myelinating forms, their size decreases. Yet another feature of dedifferentiated SCs is their ability to exert a stimulatory effect on reparative processes in various tissues [72].

Recently, it has been reported that SC precursors and Büngner band cells exhibit multipotency. For instance, in a study conducted on a mouse incisor restoration model it was established that SCs engender cells that eventually form dental pulp cells and odontoblasts [73]. The possibility for SC precursors to differentiate into melanocytes, cells of parasympathetic ganglia and dental pulp mesenchymal stem cells has been confirmed experimentally [74]. It was demonstrated that under in vitro conditions and in the presence of FGF-2 and epidermal growth factor SC precursors can be reprogrammed into multipotent cells able to generate cells resembling neurons, gliocytes and smooth muscle cells [75]. Uesaka et al. [76] showed that vegetative neurons of the enteric nervous system can derive not only from neural crest cells but also from SC precursors.

NERVE REGENERATION, PATHOLOGICAL PROLIFERATION OF SCHWANN CELLS, AND DEMYELINATION

A study of pathology of nerve conductors associated with SCs (nerve trauma, demyelinating disorders, tumors etc.) can shed light on the molecular mechanisms that regulate SC differentiation and their relationships with surrounding tissues. Following mechanical trauma, which can ensue from fractures, contusion, tumor-induced compression and other injuries, SCs dedifferentiate and get involved in reparative processes and remyelination. However, disordering (missequencing) of these processes results in irreversible changes which should necessarily be considered in surgical treatment [15, 20]. Peripheral nerve injuries often cause neuroma which prevents normal reparative regeneration of the nerve. As has been shown, multisized neuromas can arise at the proximal end of the injured nerve trunk, aside and inside of it [7, 8]. Neuroma comprises numerous myelinated and nonmyelinated nerve fibers, perineural sheathes, endoneural fibroblasts, SCs, collagen bundles of connective tissue; it also often contains local hemorrhages and inflammatory infiltrates [8]. Moreover, neuroma allows axonal growth and myelination, angiogenesis, proliferation of SCs and fibroblasts, accumulation of macrophages and mast cells to occur within it for a long time [22]. It is noteworthy that morphofunctional features of SCs in neuroma resemble those of normal SCs in the regenerating nerve. Neuroma can be used for experimental investigation of relationships among nerve fiber components.

Demyelinating disorders include multiple sclerosis, Charcot–Marie–Tooth disease and Guillain–Barré syndrome [18]. Charcot–Marie–Tooth disease is a hereditary ailment concerned with defects of the key myelination-related genes. Guillain–Barré syndrome in its manifestations

represents an acute inflammatory autoimmune disorder. Demyelination in the CNS can also be caused by *Mycobacterium leprae* which infects SCs in leprosy. A SC receptor α-dystroglycan is a *M. leaprae* binding site. Once the bacteria get into a cell, they integrate into the MAPK pathway, which regulates SC demyelination, and thus promote proliferation of SCs. As a result, there occurs an increase in the number of infected cells [77].

Among peripheral nerve tumors, both benign (schwannoma, neurofibroma, perineurioma, traumatic neuroma) and malignant (malignant peripheral nerve sheath tumor, MPNST) are distinguished [78]. Schwannomas derive from myelinating SCs and are composed almost completely of these cells. Neurofibromas contain all the peripheral nerve cell components, including SCs, fibroblasts, perineural cells, and axons [78]. Two types of neurofibromatosis are distinguished: type 1 or NF1 (Recklinghausen's disease) and type 2 (NF2). Both are autosomal dominant hereditary disorders. NF1 tumors are neurofibromas amalgamating fibroblasts, SCs, perineural cells, and mast cells [18]. Neurofibromas sometimes transform into MPNST or malignant neurofibrosarcommas [18].

A study of pathology of nerve trunks, specifically, their tumors, allows analyzing molecular mechanisms that regulate nerve homeostasis. For instance, it has been found out that one of the neuregulin isoforms is involved in the development of neurofibroma [79]. In contrast to neuregulin III-1a, which is responsible for the formation of myelinated nerve fibers and for the thickness of the myelin sheath, neuregulin III-3 does not influence the latter parameter. Using transgenic animals, it has been established that neuregulin III-3 overexpression in mice leads to an increased size of ganglia and nerves. Notably, this process acquires the characters of type 1 neurofibromatosis, as indicated by an increase in collagen fibers and the number of SCs. At the same time, the Remak bundles undergo a drastic change, namely they cease separating small-caliber axons from each other. Instead, axons become densely packed and the entire bundle of axons becomes wrapped in SCs as a single whole. Hyperproliferation of SCs and impaired axonal separation in the cytoplasm of Remak SCs are also early signs of NF1 [79]. These data, in authors' opinion, support the fact that sustained activation of nonmyelinating SCs by neuregulin synthesized in an axon can promote tumorogenesis in Remak complexes. This indicates that inhibition of axonal impulse conduction could be applicable for treating PNS tumors [79].

Diseases associated with SC proliferation (leprosy, NF1, NF2) recruit the MAP/ERK pathway. This signaling cascade is assumed to play a pivotal role in disseminating the disease throughout an organism, and that is why some authors believe that this direction of studies is most promising for developing a therapy against these ailments (along with antimicrobial therapy in the case of leprosy) [18]. Plexiform neurofibroma, more seldom schwannoma [80], gives rise to MPNST. Cellular and molecular features of schwannoma were described in 1920 by a Swedish neuropathologist Nils Ragnar Eugene Antoni [78]. He identified two types of this tumor with different histological characteristics. Both types, called Antoni A and B, were characterized in a review by Wippold et al. [78]. Type A tissue is multicellular and laminin-containing, while type B tissue is composed of multiple cystic formations, blood vessels and necrotic foci. Type A schwannoma is characterized by a high level of basal membrane proteins, such as laminin and collagen IV. As is well known, a high-molecular-weight glycoprotein laminin is produced by SCs at all developmental stages. It is exactly a specific marker that allows identification of SC-derived tumors and discriminating them from histiocytoma and fibrosarcoma [78]. Yet another SC-specific marker is a protein S100, which is also being used to diagnose SC-derived tumors. While in schwannomas it is almost ubiquitous, in neurofibromas it is expressed in some and in MPNST in single cells only [78].

A study of morphofunctional peculiarities of SCs in various diseases enables their histoblastic potentialities to be revealed under conditions of altered microsurrounding. Dissecting the molecular mechanisms of differentiation and unique plasticity of these cells in tumors and other nerve diseases, as well as analyzing the changes in signaling pathways that regulate these processes is both of general biological and practical impor-

tance for developing novel approaches to treating these diseases.

SCHWANN CELLS AND STIMULATION OF NERVE REGENERATION

In the literature devoted to the development of approaches to improve regeneration of the nervous system's organs, SCs receive considerable attention. This concerns, first of all, those experimental works that aim at a posttraumatic recovery of the spinal cord or peripheral nerves.

When analyzing various cell technologies used in recovering spinal cord injuries, Chelyshev and Viktorov [81] noted the appearance of SCs in the focus of spinal cord injury. In other words, remyelination of axons in the injured spinal cord involves not only oligodendroglia (myelin-producing cells in the CNS) but also SCs. SCs migrate towards the injured spinal cord area from peripheral neural structures upon injury-induced barrier disintegration. There is also an opinion on the involvement of residential neural spinal cord precursors that differentiate in SCs, or on the possibility of spinal cord oligodendrocytes to express SC markers under pathology. The ultimate goal of using cell technologies in treating spinal cord injuries is a recovery or the structure and function exactly of the white matter [8]. At this point, which concentrate nerve fibers, the use of SC transplantation seems quite reasonable because these cells form myelin. In the original studies conducted ten years ago both *in vivo* and *in vitro*, it was established that SCs can myelinate axons in the CNS and improve their regeneration.

In the 90s of the past century, there were carried out pioneer studies on transplantation of exogenous SCs into injured nerve trunks with the aim to improve their regeneration [82]. Initially, human SCs were transplanted into the Matrigel-filled artificial conduit connecting the ends of the transected sciatic nerve in immunodeficient mice. Using antibodies to primate cells, it was found that half of the transplanted SCs survive for 4 weeks. After cell therapy, myelinated axons in the conduit significantly outnumbered those in control. Some of the transplanted human SCs proved to be able to myelinate regenerating rat axons. At the same time, an improvement of nerve regeneration was demonstrated when SCs were introduced into a collagen conduit of the allogeneic animal [83]. A histological analysis showed that SCs retained their viability for a long time (120 days) and following transplantation migrated over a long distance from the implantation site.

Subsequently, the conduits that connected the proximal and distal nerve segments have been becoming ever more perfect [84]. Hadlock et al. [85] introduced SCs into a conduit made from the biodegradable stuff (a high-molecular-weight copolymer of lactic and glycolic acids) with inner surfaces that promoted adhesion of donor SCs. The presence of SCs in such a construct exerted a stimulatory effect on axonal growth. Later on, studies in this direction were carried out using GFP-transgenic animals as donors which allowed tracking transplanted cells [86, 87].

As noted above, SCs are a source of numerous growth and neurotrophic factors, extracellular matrix proteins, cytokines. Considering this feature, as well as the necessity of SC-produced biologically active substances for the recovery of injured nerve fibers, experimental works have appeared which used for transplantation not regular SCs but those genetically modified to produce NGF, BDNF, FGF-2, GDNF, or NT-3 [88–91]. Gene modification of SCs was carried out using different types of vectors (plasmids and viral vectors) [92]. Currently, plasmids or adenoviruses carrying the genes of certain growth factors (FRF2, VEGF, NDNF) are injected directly into the injured spinal cord [93, 94]. By the data of some authors, this method proved to be more efficient for the preservation of spinal nerves compared to transplantation of genetically modified cells [93, 94].

After it has been established that filling of various conduits (synthetic and natural) with SCs exerts a stimulatory effect on axonal growth, studies have begun on applying different stem cells (specifically mesenchymal stem cells, MSCs) in cell therapy [9–16]. For many years, the possibility of MSCs or other transplantable stem cells to differentiate into SCs and myelinate regenerating nerve fibers has been discussed. Using electron microscopy and immunohistochemical markers, it has been shown in some studies that it is possible. Experiments are being conducted now on *in vitro*

pre-differentiation of MSCs obtained from different sources into SCs before introducing them into a conduit or directly into an injured nerve.

Currently, gene and cell therapy for restoring nerve conductors is being intensely developed. At the same time, no less important research trend is exploring the responses of endogenous SCs in nerve trunks on injury and the application of cell therapy. Studies in this direction are not numerous. There is evidence that increased proliferative activity of SCs after application of experimental cell therapy correlates with an improved axonal growth [95]. Which specific factors produced by transplanted neural precursors are mitogenic for SCs is obscure. It is also unclear if proliferation of endoneural fibroblasts is increased under such exposures. Presumably, angiogenic factors produced by MSCs can improve vascularization of nerve trunks [96]. The latter is not only of great trophic importance for nerve regeneration but also promotes influx of cytokines and hormones to blood, thus affecting both endogenous cells and reparative processes in an injured nerve. There is an opinion that such growth factors as NGF or FGF can stimulate proliferation of SCs. Considering the role of SCs in axonal regeneration, stimulation specifically of SCs (as well as other nerve cell constituents) may represent a novel therapeutic strategy for restoring injured nerves.

CONCLUSION

The present review summarizes data available in the literature on the phylo- and ontogenetic origin of SCs in peripheral nerves and on their extraordinary phenotypic plasticity. Also described are those features of SCs that manifest themselves in pathology of peripheral nerves. Presently, novel strategies are aimed at improving the microsurrounding of regenerating nerves by means of bioengineered constructs which connect the proximal and distal segments of an injured nerve. For this purpose, a combination is used of additional components of the extracellular matrix, neurotrophic factors, exogenous stem and genetically modified cells which can promote axonal growth and regeneration. An application of novel gene and cell technologies as a therapy of nerve injuries requires deeper insight into the molecular and cellular processes that occur in a regenerating nerve trunk. Molecular factors and signaling pathways involved in regeneration of nerve fibers still remain understudied.

Further investigation is supposed to help understand in which direction gene and cell technologies are to be sophisticated. Also important is to elucidate the etiology and pathogenesis of neurological disorders associated with the dysfunction of SCs.

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