Journal of the Neurological Sciences 333 (2013) 68–72

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

An update on Schwann cell biology — Immunomodulation, neural regulation and other surprises

Patricia J. Armati *, Emily K. Mathey [1]

Neuroinflammation Group, Brain Mind Research Institute, The University of Sydney, Camperdown, 2050 NSW, Australia

ARTICLE INFO

Article history:
Received 21 September 2012
Received in revised form 16 January 2013
Accepted 16 January 2013
Available online 17 February 2013

Keywords:
Schwann cell
Perisynaptic Schwann cell
Bone marrow niche
Sympathetic fibres
Satellite cell
Peripheral nervous system
Haematopoietic stem cells
Pain

ABSTRACT

Schwann cells are primarily discussed in the context of their ability to form myelin. However there are many subtypes of these neural crest derived cells including satellite cells of the dorsal root ganglia and autonomic ganglia, the perisynaptic Schwann cells of the neuromuscular junction and the non-myelin forming Schwann cells which ensheathe the unmyelinated fibres of the peripheral nervous system which are about 80% of peripheral nerves. This review discusses the many functions of these Schwann cell subsets including their seminal role in axonal ensheathment, perineuronal organisation, maintenance of normal neural function, synapse formation, response to damage and repair and an increasingly recognised active role in pain syndromes.

1. Introduction

The most common cell type in the peripheral nervous system, the Schwann cell is derived during development from the neural crest. The Schwann cells or peripheral nerve neuroglia is specific to both the peripheral and autonomic nervous system [1] and can be further defined as those Schwann cells that form myelin [2], non-myelin forming Schwann cells of the peripheral nervous system [3] and autonomic nervous systems [4], perisynaptic Schwann cells [5] and the perineuronal satellite cells (PSC) of the dorsal root ganglia [6] and the autonomic ganglia [7]. The importance of these neuroglia is now highlighted by the increasing evidence of their roles in immune modulation, maintenance of normal nervous system function and responses to damage, disease and repair and their contribution to the pain spectrum [6,8]. What is particularly interesting is that these roles are wider ranging than previously recognised. The concept that neuroglia, particularly myelin-forming Schwann cells have an important, active role in neural response to immune-related insults such as that resulting from autoimmune diseases such as Guillain Barrè Syndrome (GBS) and Chronic Idiopathic Demyelinating Polyneuropathy (CIDP) was only defined in the 1970's and at the time was somewhat controversial. Among the surprising findings were reports that Schwann cells can upregulate MHC class 11 molecules, present antigen and produce cytokines of immunological importance with evidence from cell cultures and patient nerve biopsies [9–12] – see also next article – Pollard and Mathey (Fig. 1). It is also intriguing to follow the literature showing that the unmyelinated Schwann cells of the nerve terminal at the neuromuscular junction (NMJ) actively modulated synapse formation, actively responded to nerve conduction and neurotransmitter signalling as well as a role in the repair of the NMJ. The role of Schwann cells, in pain modulation and upregulation is now increasingly recognised as important.

2. Myelin forming Schwann cells

The Schwann cells that form myelin are very large cells highly specialised and actively interact with axons for normal function, maintenance and repair. Some ensheathe Aδ nociceptor fibres with relatively few compact myelin lamellae, while others form up to 100 spirals of compact myelin lamellae around the larger diameter sensory fibres. Of unknown significance was the observation by Van Geren [13] who first described the spiralling of the Schwann cell, that each Schwann cell spiral is in the opposite direction to its neighbour. Of known importance is that the axonal diameter is directly related to the number of compact myelin lamellae which directly affects the saltatory conduction velocity — the more lamellae, the faster the conduction. While the histological feature of myelinated nerve has been dominated by the compact myelin lamellae, it is now clear that the non-compact regions of the inner and outer mesaxon, the paranodal 'loops', the Schmidt Lanterman incisures, transverse processes and

* Corresponding author. Tel.: +61 413432715.
E-mail address: patricia.armati@sydney.edu.au (P.J. Armati).
[1] Tel.: +61 413432715.

0022-510X/$ – see front matter © 2013 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jns.2013.01.018

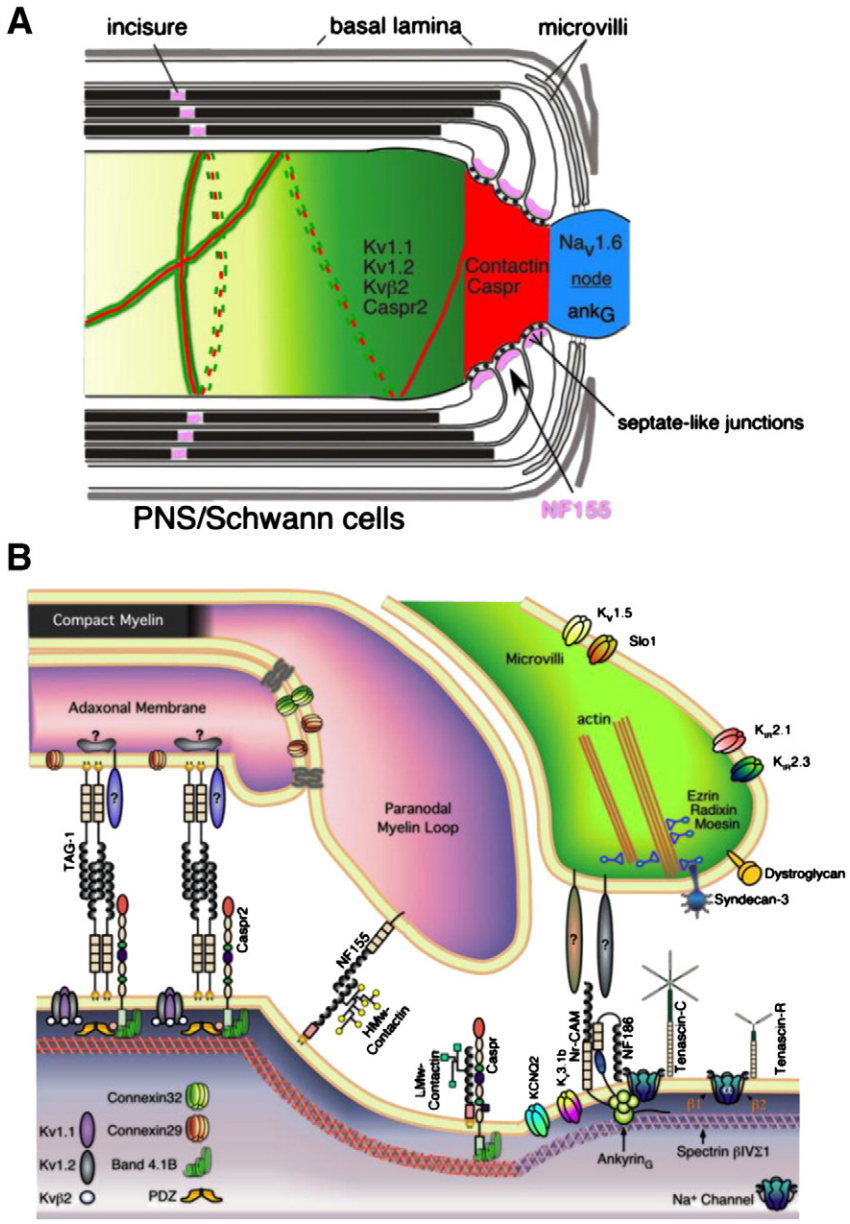

Fig. 1. Complex organisation of the myelinated Schwann cell — Scherer and Arroyo [14] with permission from Wiley [14] and Arroyo and Scherer [2] with permission from Cambridge University Press.

nodal microvilli play a pivotal role in maintaining the organisation which is pivotal for fast nerve conduction [2,10].

When the myelinated Schwann cell is damaged, it is unable to maintain its complex architecture and relationship with its axonal length. While each Schwann cell's relationship with its ensheathed axonal length is critical for normal nerve conduction, these cells are also facultative antigen presenting cells, thereby able to respond to auto and foreign antigens. Their immune responsiveness can result in demyelination and conduction block in the absence of axonal damage. Myelin-forming Schwann cells are also active in immunomodulation. They constitutively express many receptors related to immunomodulation [9], and can facultatively upregulate their expression of MHC class 1 and class 11 antigens [11].

3. Non-myelin forming Schwann cells

It is always surprising to consider that the majority of nerve fibres in peripheral nerve are unmyelinated and estimated by Griffin et al. to make up approximately 80% of peripheral nerve [3]. These Schwann cells, although ensheathing axonal lengths, do not form compact myelin but each Schwann cell has many axonal lengths embedded within grooves of its plasma membrane. Of further interest is that unmyelinated Schwann cells also express P2 nucleotide receptors through which ATP is released and taken up by axonal P2Y receptors with a resultant increase in axonal excitability nociceptors. In contrast adenosine appears to downregulate this excitability which has implications for pain modalities [15].

In contrast to the axonal ensheathing Schwann cells, satellite cells also of neural crest origin, encapsulate the nerve cell bodies of dorsal root ganglia (DRG) as well as those of sympathetic and parasympathetic ganglia, but do not form myelin. These cells are now recognised as active in normal peripheral nerve sensory/afferent function with an important role in DRG organisation and maintenance, and active response to nerve damage and repair. They provide support to neuronal cell bodies with paracrine-type signalling between the satellite cells and neuronal cell bodies [16] (Fig. 2).

The role of perineuronal satellite cells (PSCs) in pain is particularly interesting. In peripheral nerve injury, the PSCs upregulate the production of nerve growth factor (NGF), and the NGF homologue NT3 and the NT3 receptor P75 [6]; important molecules related to pain syndromes. These pain-related responses are seen in changes within the DRG commonly associated with the large diameter cell bodies rather than small diameter cell bodies which are related to the nociceptors. For example, injured peripheral nerve NT3 has been reported to upregulate sprouting of sympathetic nerves associated with blood vessels of the DRG. These neurites form baskets of fibres around cell bodies of the large diameter fibres. This basket formation has been known for some time, however was previously not known to be associated with sympathetic sprouting resulting from nerve damage promoted by NT3. Importantly, this is confirmed in both animal models of pain and in human post-mortem studies [17,18].

While PSCs can be involved in upregulation of chronic pain, there is also evidence that they can contribute to its downregulation. PSCs can also be shown to release ATP as a neurotransmitter/cotransmitter which signals bidirectionally between the satellite cell and the nerve cell body [6,19]. ATP is released from the satellite cells via P2X receptors which is then taken up via P2Y receptors on the nerve cell body. This in turn can downregulate neuronal purinergic receptors P2X and switch off nociceptor signalling [20,21]. This raises the possibility that the interaction between satellite cell and cell body could provide a new direction for therapeutic strategies.

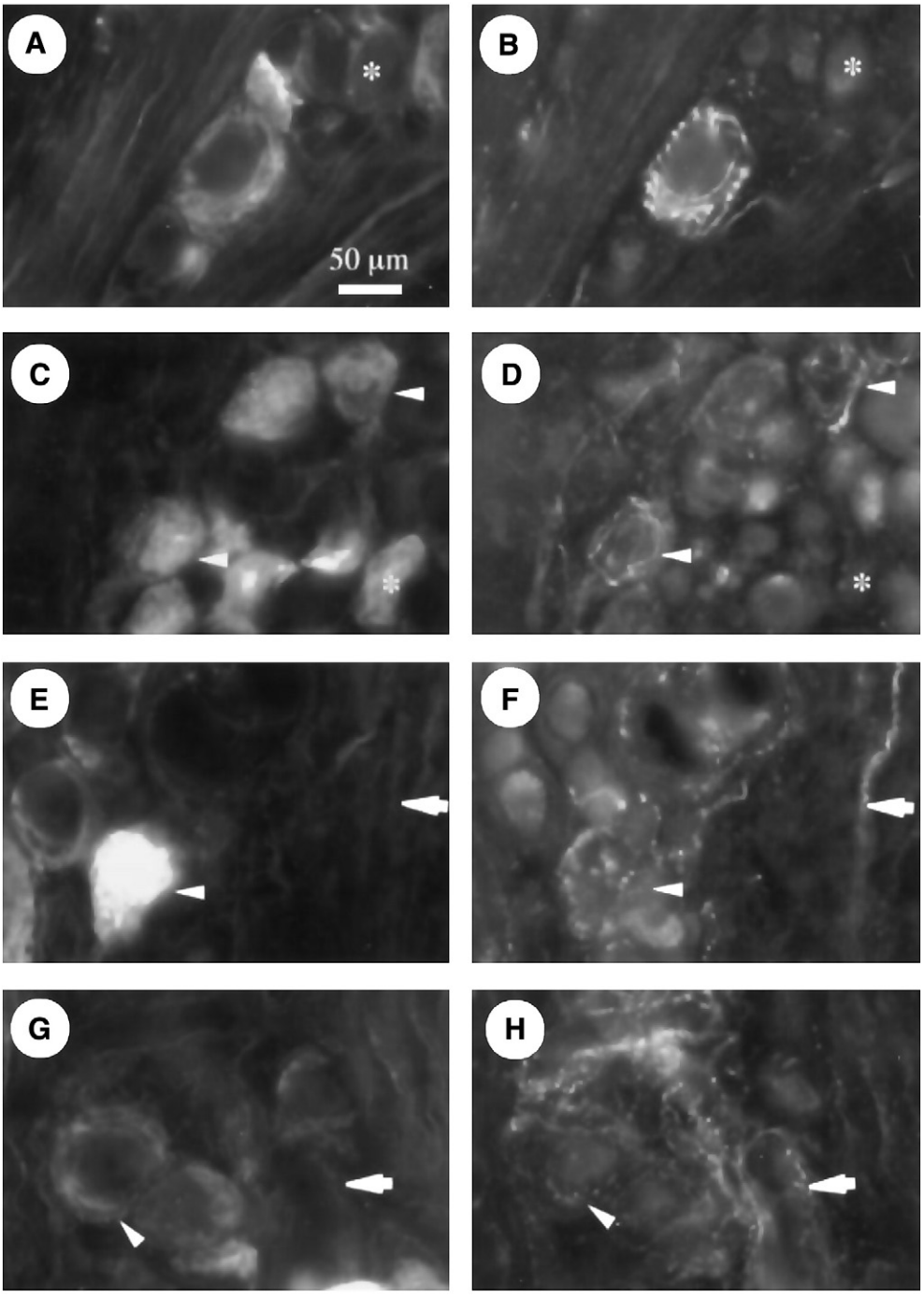

Fig. 2. Satellite cell derived nerve growth factor, neurotrophin 3 and P75 are involved in noradrenergic sprouting (arrowed) in dorsal root ganglia (Zhou et al., 1999).

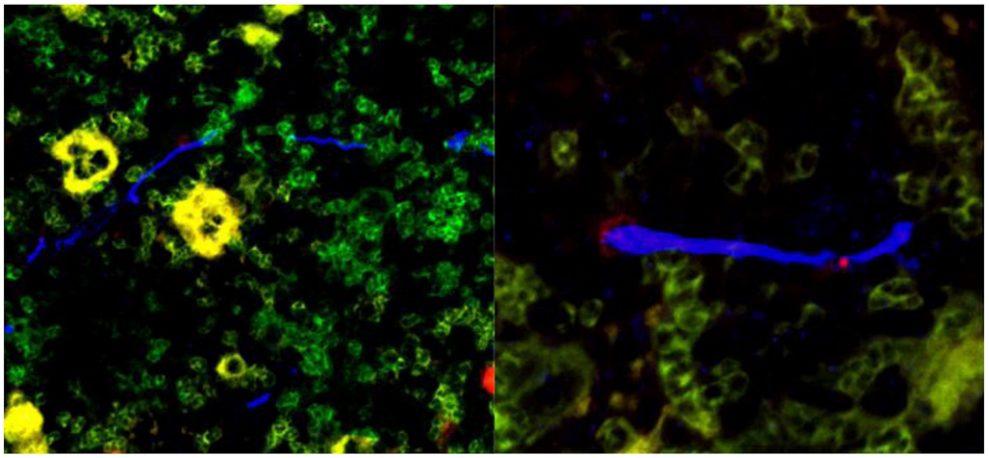

Fig. 3. Representative fluorescence micrographs of colocalizing HSCs (red). GFAP-positive glial cells (blue). Frozen wild-type BM sections were stained with anti-CD150 (red), CD48, CD41, and lineage markers (green) for HSCs, (Yamazaki et al. 2011).

4. Perisynaptic Schwann cells

The unmyelinated perisynaptic Schwann cells ensheathe the final region of motor nerve terminals at the NMJ. While their ensheathment has been well described, their essential role in organisation of the synapse, maintenance of the NMJ, neurotransmission and repair of damaged NMJ has more recently been defined. There is now evidence that these perisynaptic or terminal Schwann cells are active in the 'formation, function, maintenance and repair' of the chemical synapse of the NMJ [22]. They guide developing nerve terminals during both development and regeneration. They express many more ion channels and neurotransmitter receptors than myelinated Schwann cells, resembling central nervous system astrocytes [23]. They can detect and modulate neurotransmission and form the 3rd dynamic partner of what is more accurately termed the tripartite synapse — nerve, muscle fibre and PSCs. Interestingly they also have a synaptic signalling role with a paracrine range of millimetres rather than the metres/s of a peripheral nerve fibre. In cultures of the amphibian *Xenopus*, and of rat Schwann cells the conditioned culture medium from both contained transforming growth factor (TGF) β1. This appears to be an important factor in promoting the NMJ synapse and is also found in neonatal rat PSCs and may well promote neuronal agrin which promotes AChR clustering acting directly on the neurite rather than the muscle cell [22]. Mammalian PSCs also respond to ACh via stored Ca^{2+} which is dependent on muscarinic not nicotinic receptors. It is interesting although the significance is not understood, that these unmyelinated Schwann cells express MBP, generally a hallmark of myelinated Schwann cells [5] and have G protein-dependent depression of synaptic transmission.

5. Schwann cells of bone marrow sympathetic fibres

An interesting recent report shows that these unmyelinated Schwann cells within the bone marrow play an important role in haemopoietic stem cell (HSC) regulation. This relates to those Schwann cells ensheathing sympathetic fibres which run parallel to the blood vessels within the bone marrow (BM) niche [4,24]. The Yamazaki et al. study reported that it was these glial fibrillary associated protein (GFAP)-positive Schwann cells that were seminal in regulating the hibernation and activation states of stem cells. The Schwann cells express bone marrow niche factor genes and the TGFβ activator molecule that converts the inactive form of TGFβ present in the stem cells into the active form. This in turn may downregulate lipid raft clustering, essential for HSC activation [25,26]. It appears that the Schwann cells maintain the hibernation state of the stem cells. This also involves Smad phosphorylation interactions with TNFβ [4]. Denervation experiments resulted in the activation of the stem cells but repopulation of the niche was inhibited (Fig. 3).

This very interesting and perhaps surprising finding highlights yet again, the active and important role of neural signalling [27], now defined by Yamazaki and colleagues as the Schwann cells, effecting migration of stem cells from the bone marrow.

6. Schwann cells as potential glial stem cells

The neural crest-derived satellite cells of the dorsal root ganglia have also been shown to have potential as glial-derived stem cells. Work by Fex Svenningsen et al. [28] has shown that these cells can be induced to differentiate into other neuroglial cells including not only myelinating Schwann cells but also astrocytes and oligodendrocytes of the central nervous system. The studies were done in cultures of dissociated DRG, which may perhaps lead to a loss of signals from other cell types when dissociated. Fex et al. found that the cells constitutively express the chondroitin sulphate proteoglycan – NG_2 – characteristic of oligodendrocyte precursor cells. Interestingly the isolated cells expressed a number of oligodendrocyte precursor cells including platelet derived growth factor (PDGF). More recent work by Widera et al. [29] using palatal derived myelinating Schwann cells has shown that they expressed nestin as well as S100. In this study, the pluripotency factors Sox2, Klf4, c-Myc, Oct4, the NF-κB subunits p65, p50, and the NF-κB-inhibitor IκB-β were up-regulated in Schwann cells derived from palatal tissue. In Schwann cells derived from this source as well as from sciatic nerve could also be manipulated into multipotent neural crest phenotypes. In addition the nestin positive cells could be reprogrammed in culture to provide stem cells able to differentiate into ectoderm, mesoderm and endoderm phenotypes. Martin et al. [30] also consider Schwann cells to be a source of multipotent neural crest cells and although they consider them dormant, their active role in the normal function and maintenance of the peripheral nervous system and their response to injury makes their multitasking capability even more impressive.

References

[1] Le Douarin NM, Kalcheim C. The Neural Crest. 2nd ed. Cambridge University Press, Cambridge; 2009.
[2] Arroyo EJ, Scherer S. The molecular organisation of myelinating Schwann cells. In: Armati PJ, editor. The Biology of Schwann Cells. Cambridge: Cambridge University Press; 2007. p. 37–54.
[3] Griffin JW, Thompson WJ. Biology and pathology of nonmyelinating Schwann cells. Glia 2008;56(14):1518–31.
[4] Yamazaki S, Ema H, Karlsson G, Yamaguchi T, Miyoshi H, Shioda S, et al. Nonmyelinating Schwann cells maintain hematopoietic stem cell hibernation in the bone marrow niche. Cell Nov 23 2011;147(5):1146–58.

[5] Ko CP, Sugiura Y, Feng Z. The biology of perisynaptic (terminal) Schwann cells. In: Armati PJ, editor. The Biology of Schwann Cells. Cambridge: Cambridge University Press; 2007. p. 72–99.
[6] Zhou XF, Deng YS, Chie E, Xue Q, Zhong JH, McLachlan EM, et al. Satellite-cell-derived nerve growth factor and neurotrophin-3 are involved in noradrenergic sprouting in the dorsal root ganglia following peripheral nerve injury in the rat. Eur J Neurosci May 1999;11(5):1711–22.
[7] Schwyn RC. An autoradiographic study of satellite cells in autonomic ganglia. Am J Anat 1967;121:727–40.
[8] Zhou XF, Deng YS, Xian CJ, Zhong JH. Neurotrophins from dorsal root ganglia trigger allodynia after spinal nerve injury in rats. Eur J Neurosci Jan 2000;12(1):100–5.
[9] Lisak RP, Benjamins JA. Cytokine and chemokine interactions with Schwann cells: the neuroimmunology of Schwann cells. In: Armati PJ, editor. The Biology of Schwann cells. Cambridge: University of Cambridge Press; 2007. p. 100–17.
[10] Pollard JD, Armati PJ. CIDP — the relevance of recent advances in Schwann cell/axonal neurobiology. J Peripher Nerv Syst Mar 2011;16(1):15–23.
[11] Armati PJ, Pollard JD, Gatenby P. Rat and human Schwann cells in vitro can synthesize and express MHC molecules. Muscle Nerve Feb 1990;13(2):106–16.
[12] Pollard JD. Chronic demyelinating polyneuropathy and Schwann cells. In: Armati PJ, editor. The Biology of Schwann Cells. Cambridge: Cambridge University Press; 2007. p. 171–84.
[13] Uzman BG, Nogueira-Graf G. Electron microscope studies of the formation of nodes of ranvier in mouse sciatic nerves. J Biophys Biochem Cytol Jul 25 1957;3(4):589–98.
[14] Scherer SS, Arroyo EJ. Recent progress on the molecular organization of myelinated axons. J Peripher Nerv Syst Mar 2002;7(1):1–12.
[15] Irnich D, Burgstahler R, Bostock H, Grafe P. ATP affects both axons and Schwann cells of unmyelinated C fibres. Pain Jun 2001;92(3):343–50.
[16] Ren K, Dubner R. Interactions between the immune and nervous systems in pain. Nat Med Nov 2010;16(11):1267–76.
[17] Shinder V, Govrin-Lippmann R, Cohen S, Belenky M, Ilin P, Fried K, et al. Structural basis of sympathetic-sensory coupling in rat and human dorsal root ganglia following peripheral nerve injury. J Neurocytol Sep 1999;28(9):743–61.
[18] Li D, Wang L, Lee CW, Dawson TA, Paterson DJ. Noradrenergic cell specific gene transfer with neuronal nitric oxide synthase reduces cardiac sympathetic neurotransmission in hypertensive rats. Hypertension Jul 2007;50(1):69–74.
[19] Zhang YQ, He LM, Xing B, Zeng X, Zeng CG, Zhang W, et al. Neurotrophin-3 gene-modified Schwann cells promote TrkC gene-modified mesenchymal stem cells to differentiate into neuron-like cells in poly(lactic-acid-co-glycolic acid) multiple-channel conduit. Cells Tissues Organs 2012;195(4):313–22.
[20] Chen Y, Zhang X, Wang C, Li G, Gu Y, Huang LY. Activation of P2X7 receptors in glial satellite cells reduces pain through downregulation of P2X3 receptors in nociceptive neurons. Proc Natl Acad Sci U S A Oct 28 2008;105(43):16773–8.
[21] Chen Y, Li G, Huang LY. P2X7 receptors in satellite glial cells mediate high functional expression of P2X3 receptors in immature dorsal root ganglion neurons. Mol Pain 2012;8:9.
[22] Feng Z, Ko CP. Schwann cells promote synaptogenesis at the neuromuscular junction via transforming growth factor-beta1. J Neurosci Sep 24 2008;28(39):9599–609.
[23] Auld DS, Robitaille R. Perisynaptic Schwann cells at the neuromuscular junction: nerve- and activity-dependent contributions to synaptic efficacy, plasticity, and reinnervation. Neuroscientist Apr 2003;9(2):144–57.
[24] Bruckner K. Blood cells need glia, too: a new role for the nervous system in the bone marrow niche. Cell Stem Cell Dec 2 2011;9(6):493–5.
[25] Yamazaki S, Iwama A, Takayanagi S, Morita Y, Eto K, Ema H, et al. Cytokine signals modulated via lipid rafts mimic niche signals and induce hibernation in hematopoietic stem cells. EMBO J Aug 9 2006;25(15):3515–23.
[26] Yamazaki S, Iwama A, Takayanagi S, Eto K, Ema H, Nakauchi H. TGF-beta as a candidate bone marrow niche signal to induce hematopoietic stem cell hibernation. Blood Feb 5 2009;113(6):1250–6.
[27] Katayama Y, Battista M, Kao WM, Hidalgo A, Peired AJ, Thomas SA, et al. Signals from the sympathetic nervous system regulate hematopoietic stem cell egress from bone marrow. Cell Jan 27 2006;124(2):407–21.
[28] Fex SA, Colman DR, Pedraza L. Satellite cells of dorsal root ganglia are multipotential glial precursors. Neuron Glia Biol Feb 2004;1(1):85–93.
[29] Widera D, Heimann P, Zander C, Imielski Y, Heidbreder M, Heilemann M, et al. Schwann cells can be reprogrammed to multipotency by culture. Stem Cells Dev Dec 2011;20(12):2053–64.
[30] Martin I, Nguyen TD, Krell V, Greiner JF, Muller J, Hauser S, et al. Generation of Schwann cell-derived multipotent neurospheres isolated from intact sciatic nerve. Stem Cell Rev Jun 5 2012;8:1178–87.