

● PERSPECTIVES

Two faces of Schwann cell dedifferentiation in peripheral neurodegenerative diseases: pro-demyelinating and axon-preservative functions

Schwann cells are glial cells that are responsible for the synthesis and maintenance of the myelin sheath in the peripheral nerve system. Under pathological conditions, such as physical nerve injury and inflammatory neuropathies, Schwann cells undergo a substantial phenotype transformation that is not related to their intended function. For example, Schwann cells dedifferentiate into immature states and thereby cease to express myelin genes after nerve injury. Dedifferentiated Schwann cells activate lysosomal and proteasomal protein degradation systems, which suggests that Schwann cells actively participate in demyelinating processes *via* the dedifferentiation process. In addition to the pro-demyelinating functions of dedifferentiated Schwann cells, they induce the expression of several neurotrophic factors that play critical roles in neuronal survival and axonal regeneration following peripheral nerve injury. The induction of neurotrophic factors by dedifferentiated Schwann cells might protect against secondary axonal damage in hereditary and immune mediated neuropathies. Therefore, the pro-demyelinating and axon-preservative functions of Schwann cells may make critical contributions to the pathophysiological processes of peripheral neuropathies. We also briefly review the mechanism of Schwann cell dedifferentiation with special emphasis to mitogen activated protein kinase and the transcription factor c-jun.

Introduction

In vertebrates, Schwann cells are glial cells that form a myelin sheath, which produces the saltatory conduction of neural impulses in the peripheral nervous system (Sherman and Brophy, 2005). In the case of abnormal myelin sheath generation due to genetic mutations or myelin sheath destruction by acquired nerve damage induced by inflammation or drugs, problems arise in the peripheral nervous system, leading to muscle atrophy or sensory disorders (Sherman and Brophy, 2005; Jessen and Mirsky, 2008). During the embryonic period, the neural crest cells migrate along with growing peripheral axons. A Schwann cell precursor that has finished migrating and has attached to a growing nerve may wrap around a few or as many as dozens of axons, but ultimately only target a single axon that requires a myelin sheath in response to a certain stimulus (Sherman and Brophy, 2005; Jessen and Mirsky, 2008). In the period of Schwann cell generation, the cell is called Schwann cell progenitor or immature Schwann cell. Subsequently, the Schwann cell begins the process of myelin-related gene expression and wraps the axon with the elongated Schwann cell membrane, which continues throughout the postnatal period to complete the myelin sheath formation (Sherman and Brophy, 2005; Jessen and Mirsky, 2008).

The mature myelin sheath will last a lifetime, except when damage, such as nerve injury, occurs. Acute and chronic demyelinating peripheral neuropathies are primary diseases that cause myelin destruction in adults (Jessen and Mirsky, 2008). When a peripheral nerve is physically severed, distal axons are completely degenerated, and the Schwann cells wrapped around the axons directly participate in the degeneration of the myelin sheath, which leads to demyelination (Jessen and Mirsky, 2008). Afterwards, macrophages that migrate from the blood assist in completely removing the degenerated axon and the myelin sheath (Martini

et al., 2008). Meanwhile, in inflammatory demyelinating diseases, acute or chronic form of demyelination may occur regardless of axonal damage, and it is considered that demyelination occurs due to local inflammation caused by autoimmune mechanisms, which may attack components of the myelin sheath or junctional regions (Pollard and Armati, 2011).

Pro-demyelinating function of Schwann cell dedifferentiation

Schwann cell dedifferentiation is a distinctive phenomenon exhibited by Schwann cells in the process of demyelination, which can be clearly observed following peripheral nerve injury (Jessen and Mirsky, 2008). Dedifferentiation is the term used when a differentiated cell retrogresses to its initial form, and during this process, a dedifferentiated Schwann cell halts the expression of myelin-related genes but re-expresses many immature Schwann cell markers. While expressing the characteristics of immature Schwann cells, dedifferentiated Schwann cells increase lysosomal and proteasomal activity, resulting in myelin destruction (Jessen and Mirsky, 2008; Lee et al., 2014) (Figure 1). Thus, a dedifferentiated Schwann cell performs an action completely opposite to its intended function by destroying the myelin sheath, instead of forming it, to rapidly remove non-reusable myelin debris following nerve injury.

Even though it has been proposed that inflammatory cells play a primary role in demyelination in hereditary or inflammatory demyelinating diseases (Pollard and Armati, 2011), dedifferentiated Schwann cells may also play an active role in demyelination through the cessation of myelin-related gene expression and lysosome activation (Figures 1, 2). In addition, because dedifferentiated Schwann cells express many inducers for monocyte chemotaxis for demyelination in an injury model (Martini et al., 2008) (Figure 2), it is possible that dedifferentiated Schwann cell-induced macrophages exist among the infiltrating cells in inflammatory regions in neuropathic nerves, in addition to autoimmune inflammatory reaction-induced macrophages. Moreover, in the peripheral nerves of a Charcot Marie Tooth (CMT) disease model, animal that undergoes the demyelination process, it is possible to delay demyelination by the inhibition of the expression of Ccl2, which originates in Schwann cells and is a macrophage chemotactic factor (Groh et al., 2010). Therefore, we suggest that dedifferentiated Schwann cells exhibit a pro-demyelinating function, not only during general nerve damage, but also in specific peripheral nerve diseases. However, no concrete research has been conducted on regarding the effects of dedifferentiated Schwann cells on the progress of peripheral nerve diseases.

Axonal trophic effects of Schwann cell dedifferentiation in peripheral nerve disorders

Following physical nerve damage, dedifferentiated Schwann cells secrete various nerve growth factors, such as glial cell-derived neurotrophic factor (GDNF) and extracellular matrix proteins, that promote nerve regeneration and the very survival of both the spinal cord motor neurons and spinal sensory neurons that contain the cell bodies of the severed axons (Jessen and Mirsky, 2008; Fontana et al., 2012; Lee et al., 2014). It has been proposed that this characteristic of Schwann cells, which is not present in immature Schwann cells, is not a dedifferentiated state but a novel third state, called a “repair cell”, and the process leading up to this state has been termed “transdifferentiation” (Arthur-Farraj et al., 2012). The expression of c-jun, a transcription factor of the AP-1 family of proteins, plays an important role in this process because c-jun controls the gene expression of GDNF and Artemin in Schwann cells (Fontana et al., 2012).

The widespread expression of Schwann cell dedifferentiation

markers has been reported in experimental demyelinating diseases as well as in human neuropathic nerve sections (Hutton et al., 2011; Klein et al., 2014) (Figure 2), and the expression of c-jun in human tissue during demyelinating peripheral nerve diseases has been recently investigated (Hutton et al., 2011). Additionally, the expression of GDNF has been reported to take place in Schwann cells during inflammatory or hereditary peripheral nerve diseases (Klein et al., 2014). Considering the function of Schwann cell c-jun and GDNF in nerve regeneration (Arthur-Farraj et al., 2012; Fontana et al., 2012), it can be reasonably anticipated that dedifferentiated Schwann cells secrete nerve regeneration factors *via* c-jun, and these factors may inhibit secondary axonal degeneration or promote the regenerative growth of damaged axons in peripheral neurodegenerative diseases (Figure 1). Recently, overexpression of c-jun has been observed in Schwann cell-type CMT models, and the inhibition of c-jun expression in this mouse model aggravates secondary axonal damage (Hantke et al., 2014). Thus, it may be assumed that Schwann cell dedifferentiation/transdifferentiation *via* c-jun is a defense mechanism intended to prevent secondary axonal damage in certain types of peripheral neuropathies. It is important to verify whether this also acts as a defense mechanism during secondary axonal damage in acute or chronic inflammatory peripheral neuropathies. For example, in axon-type acute inflammatory sensory-motor neuropathy, autoimmune antibodies attack the nodes of Ranvier causing a temporary loss of function in impulse conduction, and some severe cases accompanied secondary axonal degeneration (Pollard and Armati, 2011). Further research is necessary to determine whether Schwann cell dedifferentiation can inhibit secondary axonal degeneration and whether c-jun plays an important role in this process.

MAP kinase signaling in peripheral nerve demyelination and axonal regeneration

Recently, much research has focused on the activation and function of mitogen activated protein kinases (MAP kinases) in Schwann cell dedifferentiation (Lee et al., 2014). MAP kinases include ERK, JNK, and p38 MAP kinase, which are all activated in Schwann cells after nerve injury (Lee et al., 2014). As reported by recent studies, the ERK pathway seems to play a more distinct role in Schwann cell dedifferentiation than the JNK/p38 MAP kinase pathways (Shin et al., 2013; Lee et al., 2014). For example, the Rac-JNK-c-jun pathway appears to play a pivotal role in Schwann cell dedifferentiation into “repair cells”, which is exemplified by the production of nerve regeneration factors; however, the Ras/ERK pathway seems to be important for cytokine expression and proliferation (Shin et al., 2013; Lee et al., 2014). Nevertheless, no concrete studies regarding the molecular mechanism responsible for lysosomal increase and the decrease of myelin gene expression in Schwann cells after nerve damage have been conducted. According to Shin et al. (2013), approximately 60 percent of gene expression changes in Schwann cells following nerve injury occur independently of MAP kinases. Moreover, it appears that neither the ERK nor Rac-c-jun pathways significantly contribute to halting myelin gene expression after nerve damage (Shin et al., 2013). Therefore, an in-depth study of the molecular mechanism is necessary to investigate this process.

Unlike the actively studied relationship between Schwann cell dedifferentiation and MAP kinase activation after peripheral nerve injury, the contribution of MAP kinase activation to demyelination in inflammatory and hereditary peripheral nerve diseases is largely unknown. Moreover, it has not been determined whether the expression of c-jun or GDNF depends on the Rac-JNK or ERK pathways in inflammatory or hereditary demyelinating diseases. These studies could lead to the clinical development of preventive approaches for demyelination and secondary axonal damage in peripheral nerve diseases.

Conclusion and future perspectives

The reactions of Schwann cells in response to various types of peripheral nerve damage appear to accelerate demyelination, while making positive contributions to axonal regeneration and preservation. Development of selective therapeutic approaches based on the molecular mechanism of Schwann cell dedifferentiation may provide a significant contribution to a cure for peripheral nerve diseases in the future. Thus, considering these facts, extensive further research in this area is required.

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Jong Kuk Kim, Hye Jeong Lee, Hwan Tae Park
Department of Neurology, Mitochondria Hub Regulation Center (MHRC), College of Medicine, Dong-A University, Busan, South Korea (Kim JK)
Department of Pharmacology, Mitochondria Hub Regulation Center (MHRC), College of Medicine, Dong-A University, Busan, South Korea (Lee HJ)
Department of Physiology, Mitochondria Hub Regulation Center (MHRC), College of Medicine, Dong-A University, Busan, South Korea (Park HT)

Corresponding author: Hwan Tae Park, M.D., Ph.D.

Email: phwantae@dau.ac.kr

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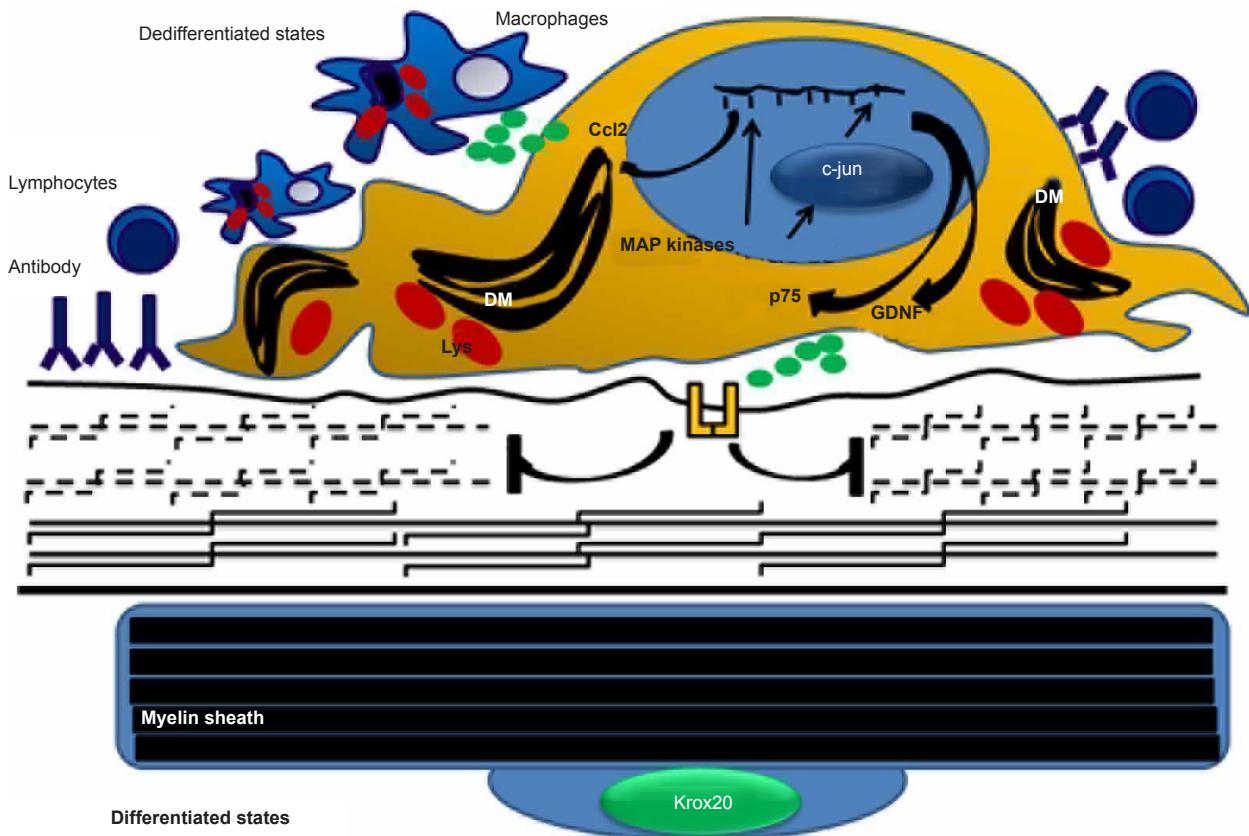


Figure 1 The figure depicts Schwann cell responses to inflammatory stimuli.

Demyelination (DM) by humoral and cytotoxic immunologic attacks in inflammatory neuropathies is accompanied by Schwann cell dedifferentiation. Dedifferentiated Schwann cells are actively participated in demyelination by upregulating lysosomal degradation systems (Lys, red-filled circles) and downregulating myelin gene expression. In addition, dedifferentiated Schwann cells produce several kinds of inflammatory cytokines including Ccl2 which induces macrophage chemotaxis. Expression of neurotrophic factors such as glial cell-derived neurotrophic factor (GDNF) in Schwann cells may be implicated in the preservation of axonal structure against secondary axonal damages. Mitogen activated protein (MAP) kinases-mediated c-jun induction is one of molecular pathways for the expression of GDNF and p75 neurotrophin receptor, a marker of dedifferentiated Schwann cells.

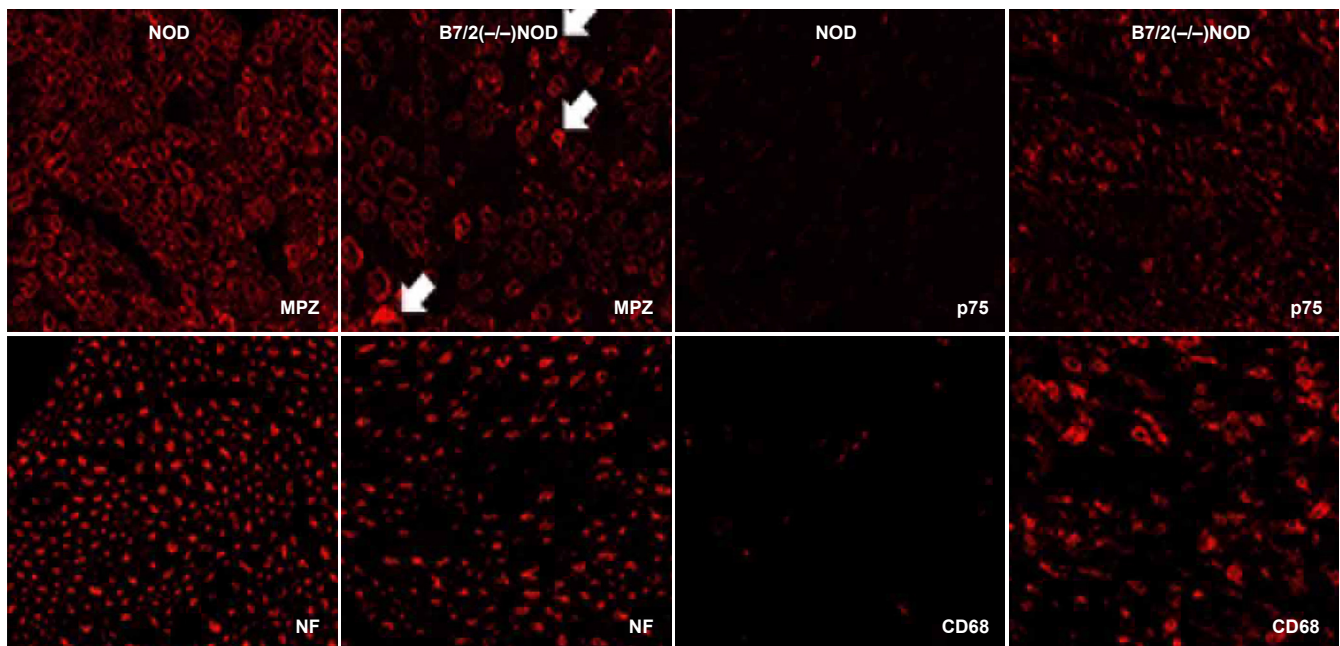


Figure 2 Representative immunofluorescent staining of sciatic nerves section from a murine inflammatory neuropathy model.

B7/2 deficient nonobese diabetic (NOD) mouse strain exhibits spontaneous autoimmune peripheral neuropathy at 20 weeks of age. Inflammatory sciatic nerves are infiltrated with numerous macrophages (CD68-positive), and most Schwann cells express p75 neurotrophin receptor indicating that Schwann cells are dedifferentiated. Degenerating myelin sheathes (stained for myelin protein zero (MPZ)) and reduced axonal density (stained for neurofilament; NF) were found in B7/2 deficient NOD nerves. Arrows indicate demyelinated axons.