ORIGINAL ARTICLE

Schwann Cells Reprogram Into Repair Phenotype Instead of Dedifferentiating to Immature Phenotype in *in Vitro* Culture

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ABSTRACT

Introduction: In vitro cultured Schwann cell has been suggested to adopt a phenotype of undifferentiated immature Schwann cells found in vivo during development. However, recent studies indicate that Schwann cells undergo cellular reprogramming into the phenotype of repair Schwann cells instead of reverting to an immature phenotype after peripheral nerve injury. The study hypothesized that in in vitro culture, Schwann cells assume the repair phenotype instead of de-differentiating to immature Schwann cells, similar to in vivo nerve injury response. Therefore, this study aimed to characterize the phenotype of cultured Schwann cells by examining the expression of classic Schwann markers and transcription factors c-Jun and Krox-20. **Methods:** Schwann cells, isolated from Wistar rat sciatic nerve, were grown in a standard Schwann cell growth medium for seven days. Then, cultured Schwann cells were analyzed using immunofluorescence analysis for classic Schwann cell markers (neurotrophin receptor p75 (p75NTR) and myelin basic protein (MBP)) and the expression profile of transcription factor c-Jun and Krox-20. **Results:** Immunofluorescence analysis revealed that cultured Schwann cells expressed a significantly high level of repair phenotype biomarkers (p75NTR and c-Jun) compared to the level of myelinating phenotype biomarkers (MBP and Krox-20). **Conclusion:** Schwann cells reprogram into repair Schwann cells instead of de-differentiating to immature Schwann cells in vitro.
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INTRODUCTION

Schwann cells are the primary glial cells in the peripheral nervous system (PNS) and play crucial roles in maintaining and supporting the functions of neurons. Schwann cells regulate neuronal viability by secretion of trophic support, axon myelination, formation of the node of Ranvier and perineurium, and conducting axonal nerve impulse [1]. Schwann cells are also involved in the injury response in the PNS by phagocytizing the damaged end of injured axons and undergoing a rapid proliferation to provide a guidance path known as Bungner's Band to aid in axonal regeneration[1].

Schwann cells originate from the neural crest cells and later become differentiated into adult Schwann cells through two intermediate stages: Schwann cell precursors (SCPs) found in early embryonic development and immature Schwann cells in late embryonic and pre-natal stages. In adult peripheral nerves, Schwann cells exist as myelin or non-myelin (Remak) Schwann cells. During maturation, immature Schwann cells differentiate into pro-myelin Schwann cells and differentiate further into mature myelinating if the Schwann cells are associated with a large diameter axon. On the other hand, immature Schwann cells, associated with small axons, transform into Remak Schwann cells which do not form the myelin sheath [2]. Both mature cells undergo drastic cellular and molecular transformations following injury, particularly at the distal denervated nerve stumps. In several previous studies, mature Schwann cells in the distal stump are thought to de-differentiate into immature Schwann cells after injury and re-differentiate into myelinating and non-myelinating Schwann cells after nerve regeneration [3–5]. However, recent findings have confirmed that mature Schwann cells, either myelinating or

Remak Schwann cells, do not revert to the immature phenotype following injury. Instead, they transform into a de novo phenotype called repair Schwann cells [6].

In vivo Schwann cells present distinct phenotypes depending on the developmental stages or wound repair phases. The phenotypes are characterized by unique expression profiles of specific biomarkers which correlate with each stage or phase the nerve tissues are in [2,7]. In various stages of Schwann cells, the expression profiles of Schwann cell-specific markers are conflicting but relatively overlapping, as shown in in vivo studies. For example, Sox10 is the only marker expressed throughout the Schwann cell development stages [2,8] while s100β is not expressed in Schwann cell precursors [9]. Immature Schwann cells and repair Schwann share similar biomolecular profiles in which both highly express L1, neural cell adhesion molecule (NCAM), p75 neurotrophin receptor (p75NTR), and glial fibrillary acidic protein (GFAP) [7], except that significant upregulation of transcription factor c-Jun is detected in repair Schwann cells following injury. Furthermore, the elevation of c-Jun is exclusively vital in Schwann cell reprogramming into repair phenotypes post-injury, but c-Jun does not play any significant functions during development [10].

Due to the highly plastic nature of Schwan cell phenotypes in native tissue, it is imperative to establish the accurate phenotypic profiles of in vitro cultured Schwann cells to affirm the fidelity and robustness of cultured Schwann cells as an experimental model for peripheral nerve studies. A previous study by Liu et al. has characterized the phenotypes of Schwann cells in culture and concluded that in vitro Schwann cells assume a state similar to undifferentiated immature Schwann cells due to the elevation of Sox2, P75NTR, NCAM, GAP43, Oct6, and MPZ expression [7]. However, the study did not analyze the expression of transcription factor c-Jun, a unique regulatory protein in repair Schwann cells. Since immature and repair Schwann cells share similar biomarker expression profiles except for c-Jun, this has raised a question of whether Schwann cells exhibit the immature or repair phenotype when grown in in vitro culture.

In this study, we hypothesize that in in vitro culture, Schwann cells assume the repair phenotype similar to in vivo Schwann cells in injured nerves instead of de-differentiating to immature Schwann cells. Therefore, to prove the hypothesis, this study aimed to characterize the phenotype of cultured Schwann cells by examining the expression of classic Schwann markers (MBP and p75NTR) and transcription factors c-Jun and Krox-20. We utilized Schwann cell culture derived from rat sciatic nerve for experimentation. The culture was then analyzed using immunofluorescence staining for classic Schwann markers (MBP and p75NTR) and transcription factors c-Jun and Krox-20. The present study's findings demonstrated that cultured Schwann cells expressed the phenotype of repair Schwann cells due to the upregulation of p75NTR and c-Jun transcription factor.

MATERIALS AND METHODS

Isolation and culture of primary Schwann cell

Male Wistar rats aged 9-12 weeks (Laboratory Animal Resource Unit, Universiti Kebangsaan Malaysia) were used in this project. All usage and handling of animals in the study were conducted per the guideline and approval by the Universiti Kuala Lumpur Animal Ethics Committee (AEC/MESTECH-UNIKL/2020/009). Primary Schwann cells were isolated from rat sciatic nerves using a previously published protocol [11]. Briefly, the sciatic nerve segment was resected by bilateral dissection and immersed in ice-cold Dulbecco's modified Eagle's medium (DMEM) D-valine containing 1% penicillin/streptomycin. Under a stereomicroscope, the epineurium was carefully removed using fine forceps. Then, the epineurium-free nerve tissue was washed with ice-cold PBS, cut into small pieces (approximately 1 mm long) using a scalpel, and digested with 0.05% collagenase-A (Sigma Aldrich) solution for 1 hour 30 minutes at 37 °C. The digested nerves were filtered using a sterile 40 µm cell strainer into DMEM D-valine containing 10% fetal bovine serum (FBS) and were then centrifuged at 1500 rpm for 6 minutes. The cell pellet was resuspended in Schwann cell growth medium containing (DMEM) d-valine supplemented with 10% fetal bovine serum (FBS) (Biosera), 1% Glutamax (Sigma-Aldrich), 1% penicillin/streptomycin (Sigma Aldrich), 0.5% Amphotericin B (Gibco), 1% N2 supplement (Gibco), 20 µg/mL bovine pituitary extract (BPE) (Sigma-Aldrich) and 5 µM forskolin (FSK) (Sigma-Aldrich). The cells will be seeded into a poly-L-lysine and laminin pre-coated 6-well plate. The cells were cultured in the Schwann cell growth medium at 37 °C with 5% CO_2. The medium was changed on day 14 and subsequently replenished every 2-3 days to confluency. For experimentation, Schwann cells were seeded at 3 x 10^4 cells per well in 24-well cell culture plates. The cells were cultured on 10 mm round glass coverslips, precoated with poly-L-lysine (Sigma-Aldrich), and incubated for seven days in the Schwann cell growth medium at 37 °C with 5% CO_2.

Immunocytochemical labeling of Schwann cells

Cells were fixed with 4% paraformaldehyde (in PBS) and permeabilized with 0.1% Triton X-100. Then, cells were blocked with 3% bovine serum albumin (BSA) in PBS for 60 minutes at room temperature. Then, the samples were incubated at 4°c overnight with

primary antibodies and washed three times with PBS before incubating with fluorescent-tagged secondary antibodies for 90 mins at room temperature. The primary antibodies used were anti-MBP (1:200, Santa Cruz Biotechnology, sc-271524), polyclonal rabbit anti s100β (1;200, Dako, Z0311), anti-p75NTR (1:200, Promega, G3231), anti-Krox20 rabbit (1:1000, Invitrogen, XC3547114), polyclonal anti-c-Jun mouse (1:200, Santa Cruz, sc-166540). The secondary antibodies used were DyLight 549-conjugated anti-mouse IgG (1:100, Vector Laboratories, cat. no. DI-2549), goat anti-rabbit IgG fluorescein (1:100, Vector Laboratories Inc, Burlingame, CA, USA, cat. no. F1-1000). The primary antibodies were diluted in 1% BSA solution, while the secondary antibodies were diluted in 1% BSA solution containing 1% goat and 1% horse serum. Lastly, Hoechst 33342 (1:200 in PBS) (Thermo Scientific) was added to stain for nuclei for 30 minutes at room temperature and washed three times with PBS before imaging. Cells were imaged using a Nikon Eclipse Ni fluorescence microscope equipped with Lumenera's Infinity 3 digital microscopy camera.

Quantitative analysis on the expression of the biomarkers using Corrected Total Cell Fluorescence (CTCF) measurement

Quantitative analysis of the biomarker expression was conducted by measuring the Corrected Total Cell Fluorescence (CTCF) using ImageJ image processing software as previously described [12]. Cells were selected individually in an image, and then the integrated density, area, and mean background fluorescence intensity were measured. The fluorescent intensity of each cell was acquired by calculating the Corrected Total Cell Fluorescence (CTCF) = integrated density – (area of selected cell x mean background fluorescence intensity) using Microsoft Excel (Microsoft 365 Apps for enterprise). The mean background fluorescence intensity was obtained from three background areas in an image to normalize against autofluorescence. 3 images were acquired for each group, with 30-40 cells measured per group.

Statistical analysis

GraphPad Prism (Version 9.0.0) was used for all statistical analyses. All data were expressed as mean ± S.D from three independent experiments. Statistical comparisons were performed by Student T-test and one-way ANOVA, with statistical significance at $p < 0.05$.

RESULTS

Immunofluorescence analysis on the expression of MBP and p75NTR in *in vitro* cultured Schwann cells

The study first characterized the phenotype of Schwann cells in in vitro culture by evaluating the expression of classic Schwann cell biomarkers MBP and p75NTR proteins through immunofluorescence analysis. Figure 1 shows representative fluorescent micrograph images of Schwann cells in in vitro culture, demonstrating positive expressions of MBP and p75NTR. p75NTR proteins (Figure 1B) were observed to be concentrated at the center mass of the cells with light distribution at the periphery. On the other hand, MBP (Figure 1D) was observed to be confined around the nucleus. Then, the study evaluated the level of MBP and p75NTR expressions by quantifying the fluorescence intensity. Figure 2 shows that the expression of p75NTR was significantly higher than MBP in cultured Schwann cells ($p < 0.05$). The mean CTCF value for p75NTR was measured at 1593997 ± 308210, which is 227.3% higher than for MBP (mean CTCF value = 487018 ± 106342).

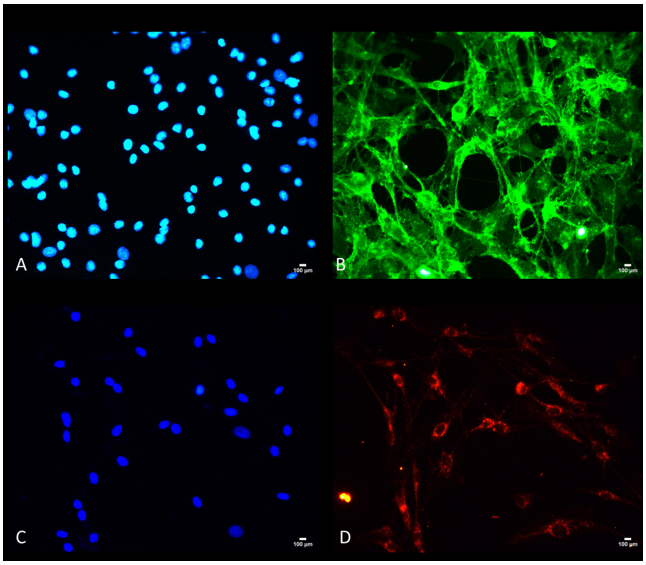

Figure 1 : Representative fluorescence micrographs of Schwann cell culture stained for (A) Hoechst; (B) p75NTR; (C) Hoechst, (D) MBP after 7 days in culture. Scale bar = 100 µm.

Immunofluorescence analysis on the expression of transcription factors c-Jun and Krox-20 in *in vitro* cultured Schwann cells

The study also examined the expression level of transcription factors, Krox-20 and c-Jun, in in vitro cultured Schwann cells. Krox-20 and c-Jun play essential roles in regulating the phenotypes of the Schwann cell. Krox-20 induces the production of myelin basic protein (MBP) and myelin protein zero (MPZ)[13], hence promoting myelination [14], while c-Jun negatively controls myelination and concomitantly enhances repair phenotypes [15]. The data shown in Figure 3, demonstrates that positive c-Jun and Krox-20 expressions were detected in cultured Schwann cells. C-Jun expression was widely distributed throughout the cytoplasm and within the nucleus (Figure 3B). There was less expression for Krox20, with the distribution mainly limited within the nucleus (Figure 3C).

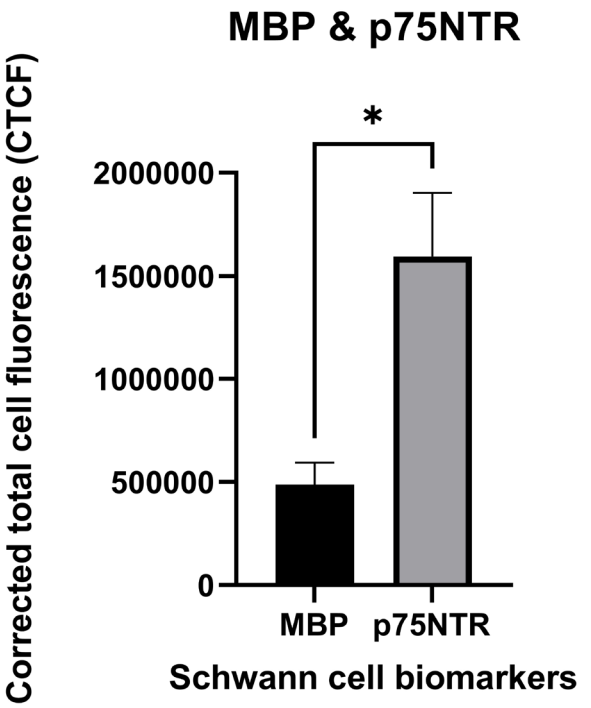

Figure 2 : Corrected total cell fluorescence measurement for MBP and P75NTR expression in Schwann cells after 7 days in culture. The fluorescence intensity of Schwann cell biomarkers was quantified to characterize the phenotype of Schwann cells. The mean CTCF value was presented as mean ± SD. (n = 3 three independent experiments).

The expression level of c-Jun and Krox-20 in Schwann cells was also quantified by measuring the fluorescence intensity, as shown in Figure 4. The expression of the c-Jun transcription factor was significantly different compared to the expression of Krox-20 (P = 0.0349). The mean CTCF value of c-Jun is 1356796 ± 214674, while the mean CTCF value of Krox-20 is 781389 ± 232704. The mean expression level of c-Jun is higher by 73.64% than that of Krox-20, indicating a significantly higher expression of c-Jun expressed than Krox-20 expression.

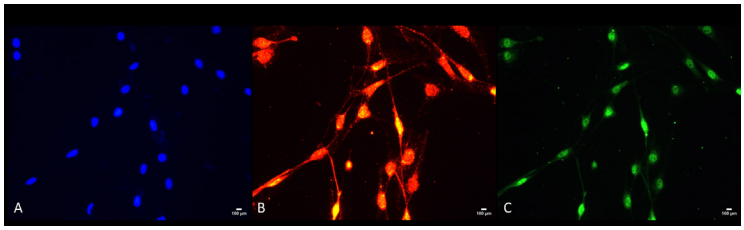

Figure 3 : Representative fluorescence micrographs of Schwann cell culture stained for (A) Hoechst; (B) c-Jun; (C) Krox-20 after 7 days in culture. Scale bar = 100 µm.

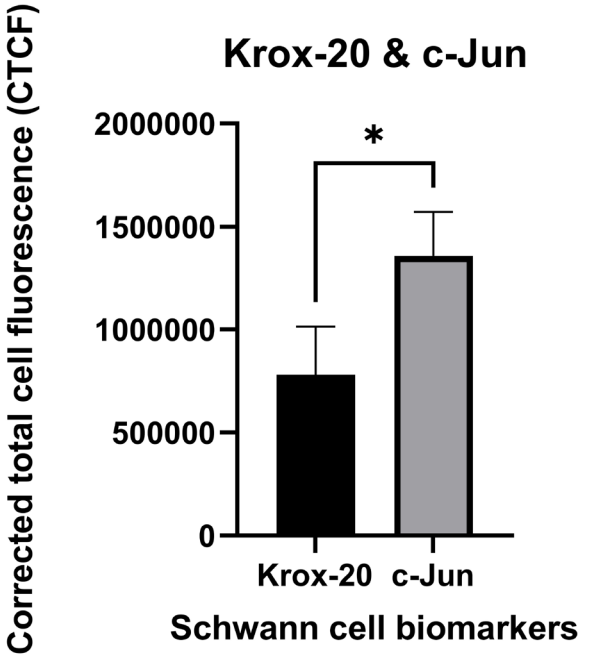

Figure 4 : Corrected total cell fluorescence measurement for the expression of transcription factor Krox-20 and c-Jun in Schwann cells after 7 days in culture. The fluorescence intensity of Schwann cell biomarkers (Krox-20 and c-Jun) was quantified to characterize the phenotype of Schwann cells. The mean CTCF value was presented as mean ± SD. (n = 3 three independent experiments).

DISCUSSION

Immature Schwann cells are prominent during development and are the precursor lineage for myelin and Remak (non-myelin) Schwann cells found in adult peripheral nerves [16]. Following injury, mature Schwann cells transform into repair phenotype, enhancing pro-regenerative characteristics thanks to Schwann cells' remarkable plasticity [17]. The study hypothesized that Schwann cells, when in culture, exhibit repair phenotype instead of de-differentiating to immature Schwann cells. To test the hypothesis, the study first characterized the phenotype of Schwann cells in culture by evaluating the expression of classic Schwann cell markers. Then, we examined the expression profiles of transcription factors implicated in the repair phenotype modulation.

Our findings demonstrated that in in vitro Schwann cells upregulated p75NTR expression, an immature Schwann cell biomarker, with concomitant downregulation of MBP expression, a myelin protein. P75NTR is a biomarker expressed by immature and non-myelinating Schwann cells. It is highly expressed in the denervated Schwann cells following injury

and in immature Schwann cells during development [18,19]. In contrast to p75NTR, MBP is one of the myelin-associated proteins and it is highly expressed in mature myelinating Schwann cells [16,20]. Thus, these results demonstrate that Schwann cells lose their mature, myelinating phenotypes in culture, potentially due to the absence of axonal contact, which is essential in the maturation and myelination of Schwann cells [21,22].

Then, the study analyzed the expression of c-Jun and Krox20, two transcription factors central in modulating Schwann cell phenotype. Krox-20 and c-Jun have an antagonistic relationship in which Krox-20 acts as the master regulator of Schwann cell myelination [23] while c-Jun negatively regulates the myelination by suppressing the functions of Krox-20 [18]. Our experiment demonstrated that the c-Jun expression level was significantly higher than the expression level of Krox-20. This finding suggests that c-Jun may suppress the expression of Krox-20 in in vitro Schwann cells, thus inhibiting myelination and causing the cells to lose their myelinating phenotype. Furthermore, c-Jun is essential in regulating the downstream molecular pathways associated with the repair cell identity, such as Olig1, and its involvement in initiating the specification of Schwann cells into repair phenotype in peripheral nerve injury response [24,25].

A previous study by Liu et al. has concluded that Schwann cells undergo de-differentiation into the immature phenotype when in in vitro culture based on the elevated expression of Sox2, $P75^{NTR}$, NCAM, GAP43, Oct6, and MPZ [7]. However, the study did not study the activity of c-Jun, the most critical transcription factor in repair Schwann cell reprogramming [10]. Interestingly, immature Schwann cells share similar characteristics with repair Schwann cells vis-a-vis the expression profile of $p75^{NTR}$ and the myelin proteins [26] except c-Jun, which is highly expressed in the latter. The elevated expression of c-Jun, as revealed in our study, has confirmed that Schwann cells do not de-differentiate into immature cells when in culture. Instead, they undergo reprogramming into repair phenotype, resembling the Wallerian process in injured in vivo nerves.

CONCLUSION

In conclusion, our study demonstrated that, in in vitro culture, Schwann cells reprogram into repair Schwann cells instead of de-differentiating to immature Schwann cells. In vitro cultured Schwann cell upregulated the expression of repair biomarkers (c-Jun and p75NTR) and concomitantly downregulated the myelinating/mature biomarkers (Krox-20 and MBP). The phenotype of cultured Schwann cells resembles repair Schwann cells in in vivo denervated peripheral nerves following injury.

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