

# Schwann Cell Caveolin-1 Expression Increases During Myelination and Decreases After Axotomy

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**ABSTRACT** The caveolins are a family of related proteins that form the structural framework of caveolae. They have been implicated in the regulation of signal transduction, cell cycle control, and cellular transport processes, particularly cholesterol trafficking. Caveolin-1 is expressed by a variety of cell types, including Schwann cells, although its expression is greatest in differentiated cell types, such as endothelial cells and adipocytes. In the present work, we characterize caveolin-1 expression both during rat sciatic nerve development and after axotomy. Schwann cells express little caveolin-1 on postnatal days 1 and 6. By P30, myelinating Schwann cells express caveolin-1, which is localized in the outer/abaxonal myelin membranes as well as intracellularly. After axotomy, Schwann cell caveolin-1 expression in the distal nerve stump decreases as Schwann cells revert to a premyelinating (p75-positive) phenotype; residual caveolin-1 within the nerve largely localizes to myelin debris and infiltrating macrophages. We speculate that caveolin-1 plays a role in the biology of myelinating Schwann cells. *GLIA* 38:191–199, 2002. © 2002 Wiley-Liss, Inc.

## INTRODUCTION

During development, Schwann cells (SC) are regulated by axon-derived signals. In embryonic nerve, SC precursors are first apparent at E14–15, giving rise to S-100-positive immature/premyelinating SC at E15–17; postnatally, these SC will give rise to myelinating and nonmyelinating SC (Jessen and Mirsky, 1991). Premyelinating SC can proliferate and are distinguished by markers such as the low-affinity nerve growth factor receptor, or p75 (Jessen and Mirsky, 1999a). As SC establish contact with large-diameter axons, they withdraw from the cell cycle and myelin synthesis ensues, with the first myelin wraps forming during the initial 24 h (Jessen and Mirsky, 1991); this stage is characterized by the expression of myelin proteins such as P<sub>0</sub> and myelin-associated glycoprotein (MAG) (Jessen et al., 1991; Webster, 1993) and the loss of p75 expression (Taniuchi et al., 1986). After nerve transection, previously myelinating SC cease to express P<sub>0</sub> and MAG and appear to revert to a dedifferentiated, premyelinating phenotype (Mirsky and Jes-

sen, 1990; S. Scherer and Asbury, 1993; S. Scherer and Salzer, 1996; Jessen and Mirsky, 1999b).

Caveolae are plasma membrane microdomains enriched in cholesterol, glycosphingolipids, signaling molecules, and the caveolins. Caveolins not only provide the structural framework of caveolae (Lisanti et al., 1993); they also regulate multiple signal transduction processes (Okamoto et al., 1998). Of the known caveolins, caveolin-1 has been most studied (Glenney and Soppet, 1992; P. Scherer et al., 1996; Tang et al., 1996). There are two caveolin-1 isoforms, 24 kDa ( $\alpha$ ) and 21

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kDa ( $\beta$ ), generated from two separate transcripts (Kogo and Fujimoto, 2000). Caveolin-1 binds to itself to form a multimeric complex (Fra et al., 1995), serving as a scaffold for a variety of signaling molecules including growth factor receptors and downstream signaling molecules (Sargiacomo et al., 1995). In many cell types, caveolin-1 levels correlate with the degree of differentiation (Fan et al., 1983; P. Scherer et al., 1995; Song et al., 1996). Cells transformed by a variety of stimuli exhibit significantly decreased caveolin-1 levels, while caveolin-1 transfection into transformed cells results in a less malignant phenotype, suggesting a growth-regulating function (Koleske et al., 1995; Lee et al., 1998; Okamoto et al., 1998).

Caveolin-1 plays a central role in the regulation of cholesterol transport, mediating its efflux in fibroblasts (Murata et al., 1995; Uittenbogaard et al., 1998). The myelin sheath is particularly enriched in cholesterol, which appears to be synthesized by the SC themselves (Fu et al., 1998). Because myelinating SC have a much greater need for cholesterol biosynthesis than do dedifferentiated SC (Goodrum, 1990), which do not synthesize myelin, it is reasonable to speculate that myelinating SC require increased caveolin-1 expression for cholesterol homeostasis.

SC are an appealing cell type in which to study the relationship between caveolin-1 expression and cell phenotype, as SC will dedifferentiate and reenter the cell cycle after axotomy (S. Scherer and Salzer, 1996). Their dedifferentiation is accompanied by a decrease in the expression of myelin-related proteins and their cognate mRNAs. We have previously shown that myelinating SC in adult rat sciatic nerve (SN) express caveolin-1 (Mikol et al., 1999). In the present study, we explore caveolin-1 expression within the context of rat SC differentiation and dedifferentiation and find that its expression is tightly linked to the myelinating phenotype.

## MATERIALS AND METHODS

### Antibodies

An affinity-purified rabbit antiserum against caveolin-1 (C13630), which recognizes both the  $\alpha$ - and the  $\beta$ -isoforms of caveolin-1, was obtained from Transduction Laboratories (Lexington, KY). The anti-S-100 $\beta$  monoclonal antibody (mAb) was purchased from Sigma (St. Louis, MO; S-2532); an anti-p75 mAb was obtained from Calbiochem (La Jolla, CA; GR10); and the ED1 mAb, which recognizes a lysosomal membrane protein of myeloid cells, particularly macrophages, was obtained from Serotec (Raleigh, NC). The anti-P<sub>0</sub> mAb and the anti-MAG antiserum were kindly provided by Drs. Juan Archelos (Max Planck Institute for Psychiatry, Munich, Germany) and James Salzer (New York University, New York), respectively.

### RT-PCR

SC were isolated from postnatal day 3 (P3) Sprague-Dawley rats (Harlan-Sprague-Dawley, Indianapolis, IN), cultured on poly-L-lysine-coated plates, and maintained in Dulbecco's modified Eagle's medium (DMEM) with 10% fetal bovine serum (FBS), supplemented with 6 mM L-glutamine, 2  $\mu$ M forskolin, and 10  $\mu$ g/ml pituitary extract (Sigma) (Brookes et al., 1979; Porter et al., 1986). Cells were grown at 37°C in a humidified atmosphere with 10% CO<sub>2</sub> and grown to ~80% confluency before cell lysates were collected. Total RNA was extracted from SC, using the guanidine isothiocyanate method (Chomczynski and Sacchi, 1987), and 2  $\mu$ g was used to synthesize cDNA with Superscript II (Gibco-BRL Products, Gaithersburg, MD). Oligonucleotides used for reverse transcriptase-polymerase chain reaction (RT-PCR) were designed such that they fell within the 5' and 3' noncoding regions of the rat caveolin-1 cDNA (Accession no. Z46614) and were common to both the  $\alpha$ - and  $\beta$ -isoforms. The oligonucleotide used for generation of template was CCTCCATCCCTGAAATGTCACCTAT, and the primers used for subsequent PCR were CATAGGATCCAGAGCCTGCAGCCAGCCACG (5') and CATAGAATTCATCCCTGAAATGTCTACTATCT (3'), with internal *Bam*HI and *Eco*RI restriction sites underlined, respectively, to facilitate cloning. For PCR amplification of cDNA template, high-fidelity *Pfu* polymerase (Stratagene, La Jolla, CA) was used. Product was restriction-digested with *Bam*HI and *Eco*RI (Boehringer-Mannheim, Indianapolis, IN), gel-extracted, and then ligated into Bluescript vector (Stratagene) that had first been digested with *Bam*HI and *Eco*RI. Clones were fully sequenced in both directions, using custom complementary primers and an automated DNA sequencer in the DNA Sequencing Core Facility at the University of Michigan.

### Immunoblotting

SN was obtained from P1, P10, P35, and P90 Sprague-Dawley rats. In some cases, the perineurium was removed before homogenization. Nerves were disrupted with a Dounce homogenizer (6–8 strokes each, loose pestle followed by tight pestle) and then sonicated for three 10-s bursts. Protein was extracted using protease and phosphatase inhibitors (Mikol et al., 1999) and quantitated using a Protein Assay kit (Bio-Rad, Richmond, CA). SN lysates were analyzed by immunoblotting after sodium dodecyl sulfate-polyacrylamide electrophoresis (SDS-PAGE) and electrical transfer of proteins onto nitrocellulose (Mikol et al., 1999). Nitrocellulose sheets were probed with an affinity-purified rabbit antiserum against caveolin-1 (1:2,500), followed by peroxidase-conjugated secondary antibodies (1:2,500; Santa Cruz Biotechnology) and visualization by enhanced chemiluminescence (ECL). We similarly prepared immunoblots of normal SN and the distal stumps of lesioned adult rat SN (12 days post-trans-

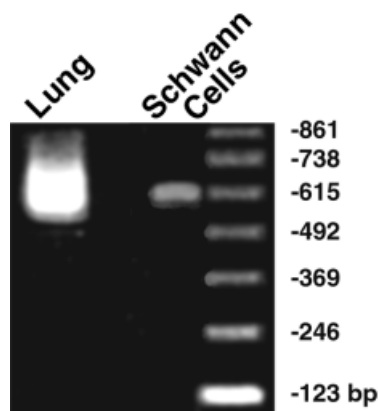


Fig. 1. Caveolin-1 mRNA expression. Reverse transcription-polymerase chain reaction (RT-PCR) (semiquantitative) of RNA from lung and Schwann cells (SC) yields a single product of ~0.6 kb in each case. Caveolin-1 mRNA is more abundant in lung than in SC. A 123-bp DNA ladder is shown on the right.

tion). Identical blots were prepared and hybridized with rabbit antisera against caveolin-1 (1:2,500) or MAG (1:2,500). Positive and negative control lysates were immunoblotted along with SN lysates, and parallel immunoblots were incubated in the absence of primary antibody (conjugate controls).

### Immunohistochemistry

SN were removed from P1, P6, P30, and P90 Sprague-Dawley rats and frozen in OCT compound (Ted Pella, Redding, CA). The distal stumps of adult nerves were similarly collected 12 days post-axotomy (transection). Sections were first fixed in 4% paraformaldehyde and then immunostained as previously described (Mikol et al., 1999). Antibodies against caveolin-1, S-100 $\beta$ , ED1, and P<sub>0</sub> were all used at 1:500. Cy-3- and fluorescein isothionate (FITC)-conjugated secondary antisera (Jackson ImmunoResearch, Westgrove, PA) were used at 1:100. Conjugate controls were done in parallel. Slides were coverslipped and viewed by fluorescence microscopy using a Leitz fluorovert microscope (W. Nuhsbaum, McHenry, IL).

## RESULTS

### Expression of Caveolin-1 in Developing Sciatic Nerve

We demonstrated previously that caveolin-1 is present in rat SC, using affinity-purified antibodies (Mikol et al., 1999). To show that SC express caveolin-1 mRNA, we performed RT-PCR on RNA from cultured rat SC with the high-fidelity polymerase *Pfu* (Fig. 1). Upon sequencing two clones from two different RT-PCR reactions, we obtained the identical sequence, which matches that for rat caveolin-1  $\alpha$  in the GenBank database (Accession no. Z46614), except for a

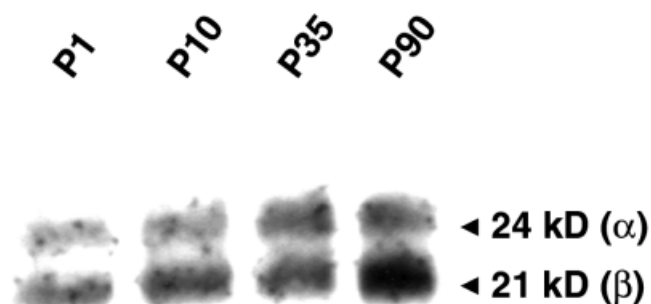


Fig. 2. Immunoblot analysis of caveolin-1 expression in developing sciatic nerve (SN). Lysates of whole rat SN obtained at P1, P10, P35, and P90 (40  $\mu$ g each) were immunoblotted with an anti-caveolin-1 antiserum. Both caveolin-1  $\alpha$  (24 kDa) and  $\beta$  (21 kDa) isoforms increase modestly during development.

single nucleotide difference (G<sub>387</sub>→C) that would be predicted to cause a Gly<sub>120</sub> → Ala substitution. This difference may represent a polymorphism, as we have cloned caveolin-1 from Sprague-Dawley rats, while the reported GenBank sequence was derived from a Norway rat. We detected only caveolin-1  $\alpha$  in cultured SC.

Because caveolin-1 expression increases during differentiation of many cell types (Fan et al., 1983; P. Scherer et al., 1995; Song et al., 1996), we wished to determine whether caveolin-1 expression by SC increases during myelination. Whereas the 8% acrylamide gels we previously used did not separate the two caveolin-1 isoforms, these were resolved on 12% gels. Immunoblot analysis of whole SN from P1, P10, P35, and P90 rats is shown in Figure 2.

Qualitatively, caveolin-1 content increases modestly at best during development; however, any change in SC-derived caveolin-1 could be obscured by the presence of substantial caveolin-1 from perineurium and blood vessels at all ages (Reale et al., 1975; Lisanti et al., 1994; Mikol et al., 1999).

Given these possible limitations of immunoblot analysis, we examined caveolin-1 expression by immunofluorescence. For this purpose, sections of rat SN obtained at ages similar to those used for immunoblotting were double-labeled for caveolin-1 and P<sub>0</sub>. This analysis was performed three times; the temporal progression of caveolin-1 expression and its spatial relationship to P<sub>0</sub> are best illustrated in transverse sections (Fig. 3). At P1, caveolin-1 is expressed minimally within the endoneurium, but there is prominent staining of blood vessels and perineurium, which persists at all ages examined. P<sub>0</sub> staining is relatively weak at P1, reflecting sparse myelination; P<sub>0</sub> and caveolin-1 do not overlap. At P6, caveolin-1 expression by SC becomes apparent. In some instances, it closely opposes or surrounds the P<sub>0</sub>-positive myelin sheaths. Caveolin-1 staining of myelinating SC is widespread at P30, when myelination is essentially complete (Hahn et al., 1987). Between P30 and P90, we did not appreciate a change in either the amount of caveolin-1 expression or its localization in myelinating SC: caveolin-1 is present



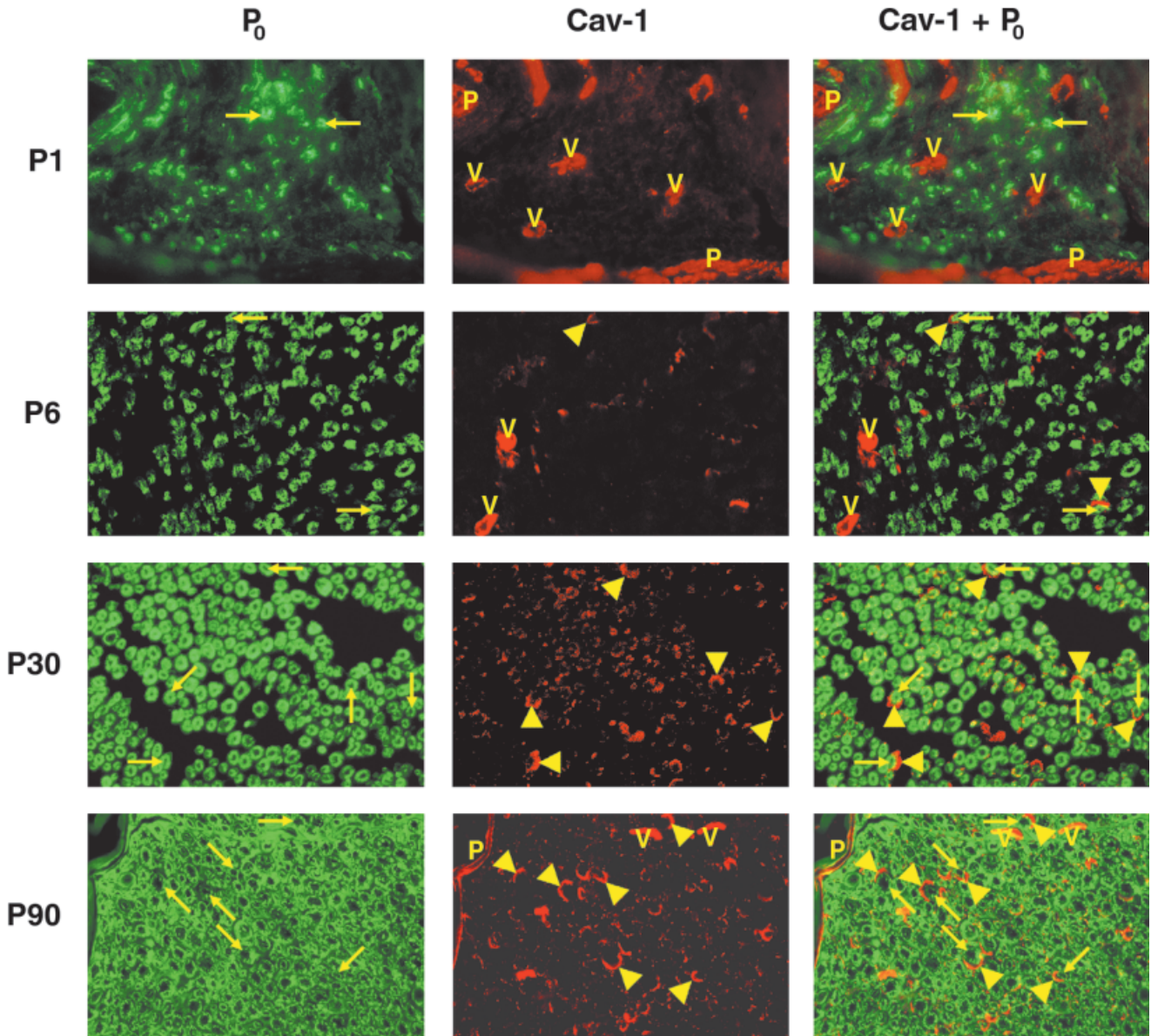


Fig. 3. Localization of caveolin-1 in developing sciatic nerve (SN). Transverse sections of P1 (A–C), P6 (D–F), P30 (G–I), and P90 (J–L) rat SN were double immunostained with a rabbit antiserum against caveolin-1 (B,E,H,K), an anti- $P_0$  monoclonal antibody (mAb) (A,D,G,J), or both (C,F,I,L). At P1 and P6, caveolin-1 is

mainly localized to the endoneurial blood vessels (V) and perineurium (P); the  $P_0$ -positive myelin sheaths (arrows) are not stained. At P30 and P90, caveolin-1 localizes to the Schwann cell (SC) bodies and abaxonal membranes (arrowheads). Scale bar = 20  $\mu$ M.

largely in abaxonal membranes and in regions within the SC that surround  $P_0$ -positive myelin sheaths.

### Expression of Caveolin-1 in Degenerating Nerve

To investigate caveolin-1 expression in axotomized nerve, distal nerve stumps were collected 12 days after axotomy, because previous work has shown that at this time SC have largely reverted to a premyelinating phenotype (S. Scherer et al., 1995). We performed immunoblot analysis using perineurium-free SN, hypothesizing that any change in SC caveolin-1 expression

would be more apparent if the non-SC content of SN were minimized. Although one cannot remove the endoneurial blood vessels, much of the perineurium can be removed from adult SN. As shown in Figure 4, there is a clear decrease in the caveolin-1 content of perineurium-free SN after axotomy, especially regarding the  $\alpha$ -isoform; this finding was confirmed by performing the experiment three times. For comparison, we examined the level of MAG in normal and transected nerve by immunoblot analysis; as expected, MAG levels decrease after axotomy (Fig. 4).

Immunohistochemical analysis of transected nerve provides more dramatic results. As shown in Figure 5,

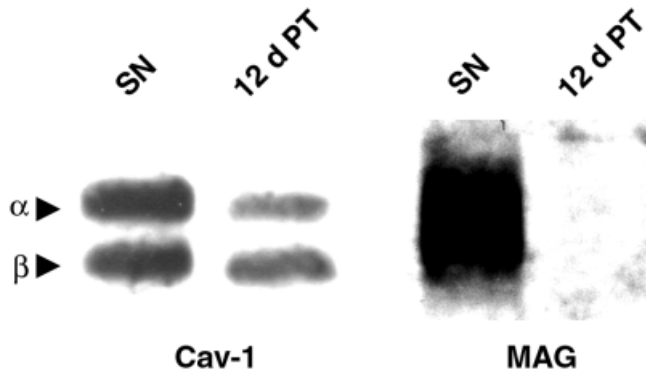


Fig. 4. Immunoblot analysis of perineurium-free sciatic nerve (SN). Lysates were prepared from an adult rat (P90) SN and an adult rat 12 days post-transection (12d PT); the nerves were stripped of perineurium to enrich for proteins expressed by Schwann cells. Two identical blots (using 40  $\mu$ g lysate per lane) were prepared and probed with rabbit antisera against caveolin-1 (Cav-1) and myelin-associated glycoprotein (MAG). Whereas the level of MAG (~100 kDa) is markedly decreased after axotomy, the level of caveolin-1 is less diminished, especially the  $\beta$ -isoform. The experiment was performed three times with similar results.

12 days after axotomy, P<sub>0</sub> is localized to the degenerating myelin sheaths, which are found in macrophages (Griffin et al., 1993). Caveolin-1 is also extremely reduced; the linear appearance of caveolin-1 immunoreactivity seen in longitudinal sections of normal nerve (Mikol et al., 1999) is absent. Some caveolin-1 staining colocalizes with P<sub>0</sub>-positive myelin debris, suggesting that it is localized in macrophages, which we directly confirmed by double-labeling sections for caveolin-1 and ED1, a marker of macrophages (Fig. 6). This caveolin-1 could have originated within the macrophages themselves (Matveev et al., 1999), or it could reflect residual caveolin-1 from phagocytosed myelinating SCs, as previously noted for periaxin, a membrane-associated protein expressed by myelinating SCs (S. Scherer et al., 1995). It should be noted that there was no apparent change in caveolin-1 immunoreactivity of blood vessels and perineurium during development or after axotomy.

In further characterizing changes in caveolin-1 expression after axotomy, we compared caveolin-1 localization with that of p75. In adult rat SN, only nonmyelinating SC express p75 (Jessen and Mirsky, 1992; Jessen et al., 1994). However, in distal stumps obtained 12 days after transection, p75-positive "denervated" SC are numerous, allowing direct comparison between the expression patterns of caveolin-1 and p75 (Fig. 5G,H). In all instances, p75-positive membranes are negative for caveolin-1-immunoreactivity. Thus, in contrast to myelinating SC, "denervated" SC do not express significant caveolin-1.

## DISCUSSION

We have confirmed and extended our previous findings that SCs express caveolin-1 (Mikol et al., 1999).

We have cloned and sequenced caveolin-1 cDNA from cultured rat SC. Although immunoblot analysis demonstrates only a modest increase in caveolin-1 during postnatal development (owing to abundant caveolin-1 expression by blood vessels and perineurium), immunostaining demonstrates a progressive increase in caveolin-1 expression during myelination, slightly lagging P<sub>0</sub> expression. Caveolin-1 is localized to the outer/abaxonal SC membrane and within SCs (surrounding compact myelin). After axotomy, residual caveolin-1 expression in axotomized nerve is mainly associated with myelin debris and macrophages.

## Myelinating SC Express Caveolin-1

The above data document that caveolin-1 protein expression is fundamentally linked to the myelinating phenotype of SC. Caveolin-1 is found in myelinating SC, but not in premyelinating SC in early postnatal development or in denervated SC after nerve transection. This pattern of expression has been observed for many other myelin-related proteins, including P<sub>0</sub>, PMP22, MBP, MAG, connexin32, periaxin,  $\beta$ 4 integrin, and Egr-2/Krox20 (Feltri et al., 1994; S. Scherer and Asbury, 1993; S. Scherer et al., 1995; S. Scherer and Salzer, 1996; S. Scherer, 1997; Mirsky and Jessen, 1990, 1999; Jessen et al., 1999; Notterpek et al., 1999), and has been taken as evidence that (1) the protein plays an important role in myelinating SC; and (2) axon-SC interactions are required to maintain expression (S. Scherer et al., 1996).

## Caveolin-1 and Proliferation

The expression of caveolin-1 expression in myelinating SC is consistent with the theme that its expression correlates with the level of cellular differentiation (Fan et al., 1983; P. Scherer et al., 1994, 1995; Mikol et al., 1999). For example, caveolin-1 is induced 25-fold when NIH 3T3-L1 fibroblasts differentiate into adipocytes, and in a variety of transformed cells its levels correlate inversely with the degree of oncogenic transformation and anchorage-independent growth (Koleske et al., 1995; Engelman et al., 1997; Lee et al., 1998). After a period of active proliferation of SC precursors during development, SC that associate with large axons cease dividing and form a myelin sheath (Jessen and Mirsky, 1991). After axotomy, SC revert to a precursor phenotype; i.e., they become P<sub>0</sub>-negative and p75-positive and reenter the cell cycle (Jessen and Mirsky, 1991; Jessen and Mirsky, 1992). Within this context, it may be relevant that caveolin-1 can suppress proliferation (Fielding et al., 1999; Bist et al., 2000). Caveolin-1 also modulates a variety of signal transduction pathways, largely functioning as a negative regulator of signal transduction. Caveolin-1 reduces signaling through the erbB2/neu receptor (Engelman et al., 1998b) and its downstream effectors, phosphatidylinositol 3-kinase



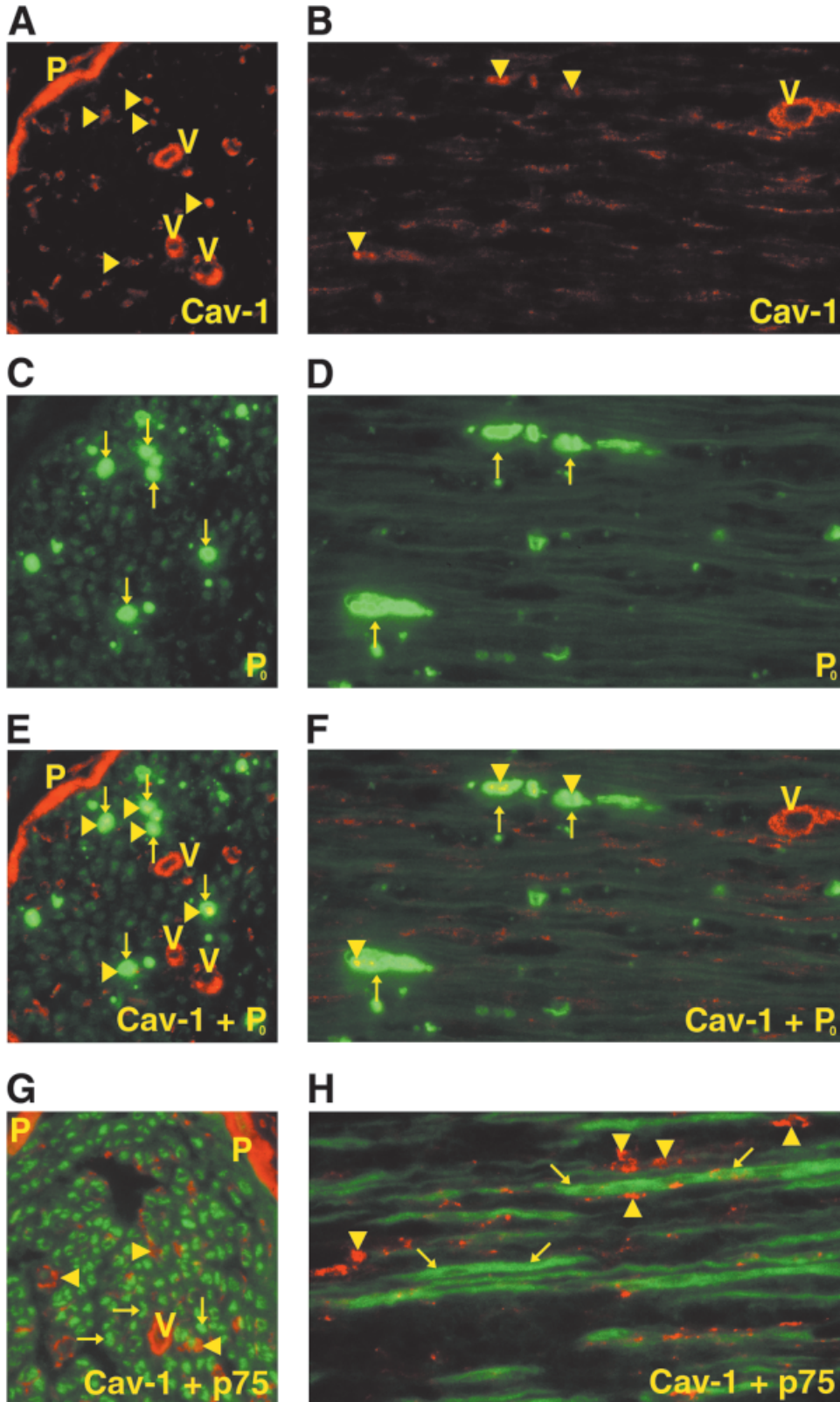


Fig. 5. Denervated Schwann cells (SCs) do not express caveolin-1. These are photomicrographs of transverse (A,C,E,G) and longitudinal (B,D,F,H) sections of rat sciatic nerve (SN) 12 days after axotomy, immunostained for either caveolin-1 (A,B), P<sub>0</sub> (C,D), caveolin-1 and P<sub>0</sub> (E,F), or caveolin-1 and p75 (G,H). Compared with intact adult nerve (Fig. 3), caveolin-1 expression within the endoneurium is markedly decreased (arrowheads), and in some cases colocalizes with P<sub>0</sub>-positive myelin debris (arrows, A-F). In contrast, caveolin-1 immunoreactivity within perineurium (P) and endoneurial blood vessels (V) remains intense. As G and H illustrate, caveolin-1 (arrowheads) and p75 (arrows) are not co-localized, indicating that denervated SC do not express caveolin-1. Scale bar = 20 μM.

(Zundel et al., 2000) and mitogen-activated protein kinase (Engelman et al., 1997, 1998a) activity, all of which have been implicated in proliferation and sur-

vival of SC (Baek and Kim, 1998; Delaney et al., 1999; Cheng et al., 2000; Garratt et al., 2000; Maurel and Salzer, 2000). Thus, the loss of caveolin-1 expression by

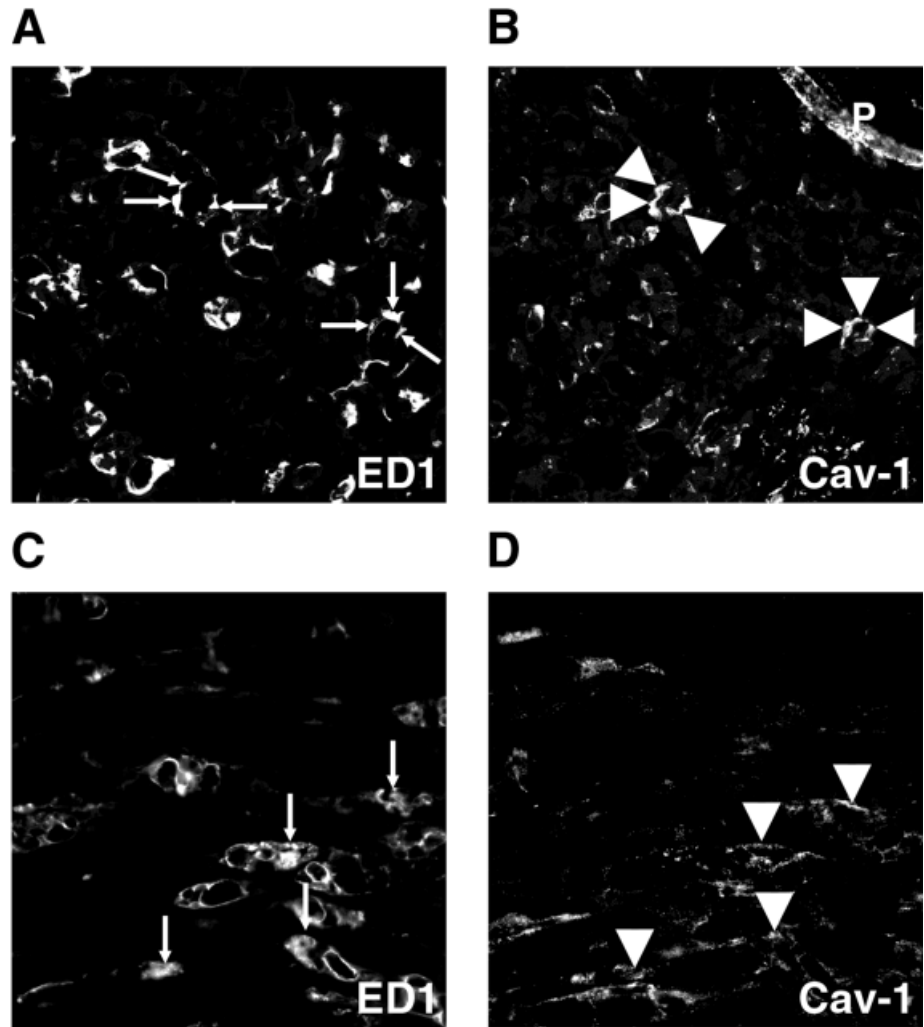


Fig. 6. Residual caveolin-1 is localized to macrophages. Photomicrographs of transverse (**A,B**) and longitudinal (**C,D**) sections of rat sciatic nerve (SN) 12 days after axotomy, immunostained with an ED1 mAb that recognizes macrophages (**A,C**) or rabbit antiserum against caveolin-1 (**B,D**). Residual caveolin-1 (arrowheads) partially colocalizes with ED1 (arrows), indicative of macrophages that have infiltrated the nerve. Scale bar = 20  $\mu$ M.

SC after axotomy may enable dedifferentiated SC to proliferate.

### Caveolin-1 and Cholesterol

Another possible role of caveolin-1 in myelinating SC relates to the regulation of cholesterol transport. Cholesterol synthesis by SC increases during myelination and decreases when SC dedifferentiate (Goodrum, 1990). Caveolae are highly enriched in cholesterol (Simionescu et al., 1983), and the structure and function of caveolae are dependent on membrane cholesterol (Li et al., 1996; Hailstones et al., 1998; Rothberg et al., 1990, 1992). Caveolin-1 itself is a cholesterol-binding protein (Murata et al., 1995), mediating cholesterol transport from the Golgi network to the plasma membrane in fibroblasts (Fielding et al., 1995; Fielding and Fielding, 1997) and cooperating with the high-density lipoprotein-binding protein SR-B1 (which is enriched in caveolae) in maintaining cholesterol homeostasis (Matveev et al., 1999). While it is not yet

clear what factors regulate caveolin-1 levels in SC, in non-neural cells cellular cholesterol concentration is critical. In fibroblasts, caveolin-1 expression varies inversely with the cellular free sterol level in order to facilitate cholesterol efflux as concentrations rise (Fielding et al., 1995, 1997; Fielding and Fielding, 1997); further, reciprocal changes in caveolin-1 and cholesterol have been identified during cell cycle progression (Fielding et al., 1999; Bist et al., 2000). Recent work has identified sterol regulatory element-like sequences and overlapping E2F- and Sp1-like sequences in the promoter region of caveolin-1 (Bist et al., 1997; Fu et al., 1998), the latter of which are known to have important effects in control of cell cycle regulation; deletion of this region abolishes cell cycle dependent changes in caveolin-1 expression (Fielding et al., 1999; Bist et al., 2000).

These findings are interesting in light of previous work that has shown that tellurium, an inhibitor of cholesterol biosynthesis at the squalene epoxidase step, causes reversible peripheral nerve demyelination in young rats, accompanied by downregulation of my-

elin proteins, upregulation of p75, and SC proliferation, as SC revert to a precursor phenotype (Wagner-Recio et al., 1991; Toews et al., 1992). The rather selective toxicity to peripheral nerve has been attributed to the relative demands for cholesterol synthesis, with myelin synthesis proceeding rapidly in the peripheral nerves of weanling rats. It has been assumed that the demyelinating effect of cholesterol lowering in myelinating SC is direct, i.e., caused by structural factors, although an intriguing possibility is that cholesterol lowering results in decreased caveolin-1 expression, SC dedifferentiation and proliferation, and subsequent demyelination. Given that caveolin-1 and cholesterol may together regulate cell cycle regulation, caveolin-1 upregulation in myelinating SC is consistent with its potential role in differentiating and cholesterol transport, while its downregulation in the setting of demyelination may enable dedifferentiation and cell proliferation. To our knowledge, caveolin-1 expression has not been studied in the tellurium model of demyelination.

Compelling evidence for a link between cellular cholesterol homeostasis and caveolin expression in vivo comes from research on Niemann-Pick type C (NPC) disease, which in humans causes a progressive demyelinating disorder. Mutations in the murine *NPC* gene lead to altered expression of NPC1, a membrane protein that has a cholesterol-sensing domain (Garver et al., 1997). Homozygotes lacking NPC1 exhibit greatly increased free cholesterol levels and a slight increase in caveolin-1 expression, while heterozygotes show near-normal cholesterol levels but greatly increased caveolin-1, the latter presumably reflecting a compensatory response to maintain cholesterol balance that homozygotes are not able to withstand in light of significantly elevated free cholesterol and absent NPC1.

Taken together with our data, these findings suggest an intimate connection between caveolin-1 expression and SC phenotype. We hypothesize that caveolin-1 plays an important role in myelinating SC, such as regulation of signal transduction, cell cycle control, and growth regulation and/or cholesterol transport. Future work will investigate the molecular mechanisms whereby caveolin-1 modulates SC phenotype.

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