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Homeobox gene expression in adult dorsal root ganglia during sciatic nerve regeneration: is regeneration a recapitulation of development?

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Abstract

After damage of the sciatic nerve, a regeneration process is initiated. Neurons in the dorsal root ganglion regrow their axons and functional connections. The molecular mechanisms of this neuronal regenerative process have remained elusive, but a relationship with developmental processes has been conceived. This chapter discusses the applicability of the developmental hypothesis of regeneration to the dorsal root ganglion; this hypothesis states that regeneration of dorsal root ganglion neurons is a recapitulation of development. We present data on changes in gene expression upon sciatic nerve damage, and the expression and function of homeobox genes. This class of transcription factors plays a role in neuronal development. Based on these data, it is concluded that the hypothesis does not hold for dorsal root ganglion neurons, and that regeneration-specific mechanisms exist. Cytokines and the associated Jak/STAT (janus kinase/signal transducer and activator of transcription) signal transduction pathway emerge as constituents of a regeneration-specific mechanism. This mechanism may be the basis of pharmacological strategies to stimulate regeneration.

Keywords: Sciatic nerve crush; Regeneration; Development; Homeobox; Transcription factor; Dorsal root ganglion

1. Introduction

Neurons of the peripheral nervous system are able to regenerate their peripheral axons after injury. The sciatic nerve, innervating the hindpaw of the animal, is frequently used to study peripheral nerve regeneration. After crush injury, the fibers distal to the lesion undergo Wallerian degeneration: the axon and myelin degenerate and are ingested by Schwann cells and invading macrophages. Schwann cells surrounding the distal fibers proliferate so that the endoneurial tubes surrounding the original nerve fibers remain intact, providing the environment through which the regenerating axons can grow (Bridge et al., 1994; Fawcett and Keynes, 1990). Axons begin to regenerate within a few hours after the crush lesion. Fibers in the proximal nerve stump start to sprout and new axons extend through the distal endoneurial tube to reinnervate their target organs (Allt, 1976; Fawcett and Keynes, 1990; Fu and Gordon, 1997; Stoll et al., 2002). In the course of regeneration Schwann cells remyelinate, a process that is dependent on contact with regrowing axons. Finally, functional recovery—this is, the return of sensory and motor functions—occurs (Bridge et al., 1994; De Koning and Gispen, 1987).

The molecular events that drive the damaged nerve through a repair program have remained elusive. As we discussed below, changes in levels or activity of specific proteins have been established and associated with the morphological transition during repair. However, the complex processes enrolling in the regenerating sciatic nerve have been compared to those that take place during development. Here, we provide an overview over the molecular changes during regeneration of the sciatic nerve, and we discuss recent data on the role that homeobox transcription factors may have in the reinitiation of developmental mechanisms during regeneration.

2. Morphological and molecular response of nerve cells to injury

Injury to the nerve fibers triggers morphological and molecular alterations in many cells. These concern dorsal root ganglion neurons and satellite cells in the dorsal root

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ganglia, and Schwann cells, endothelial cells, macrophages and fibroblasts in the (distal) sciatic nerve. In the past years, many groups have investigated alterations in expression of genes after lesioning the sciatic nerve. Cytoskeletal proteins, neurotransmitters (and/or neurotransmitter enzymes), adhesion molecules, growth factors, cytokines, transcription factors and many more protein families undergo transcriptional alterations after nerve damage (for a review, see Fu and Gordon, 1997). In Table 1, the regeneration-associated alterations in gene expression in specific cell types are summarized. In the following sections, we will focus on the reaction to injury of Schwann cells and dorsal root ganglion neurons.

2.1. Distal Schwann cells adopt a developmental phenotype

Upon nerve injury, Schwann cells distal to the lesion site lose their contact with the nerve fibers. The distal Schwann cells revert to a less differentiated state. They demyelinate and proliferate, providing a guidance substrate for growing axons (Bosse et al., 2001). This dedifferentiation has not only been shown morphologically, but is also reflected by the changes in gene expression that occur in distal Schwann cells after injury (Fig. 1; Table 1). For instance, the myelin genes P0, myelin-associated glycoprotein (MAG) and the myelin basic proteins (MBPs) are downregulated after injury. The embryonic expression patterns of extracellular matrix proteins tenascin and fibronectin are reinduced (Probstmeier et al., 2001; Vogelezang et al., 1999) and the cell adhesion molecules L1 and neural cell adhesion molecule (NCAM) are upregulated (Tacke and Martini, 1990). Neurotrophin production by Schwann cells is also reinduced after nerve crush (Lindsay, 1992; Verge et al., 1996) (Table 1). Because of these changes, it is generally accepted that Schwann cells repeat their developmental program after nerve injury. This was further supported by studies on homeobox genes, transcription factors that play important roles in the development of the nervous system (Chalepakis et al., 1993; Duboule, 1994; He et al., 1989; Hobert and Westphal, 2000). Schwann cells in the distal stump re-express the POU class homeobox gene *Oct6/SCIP* (Gondré et al., 1998; Scherer et al., 1994) and the paired class gene *Pax3* (Küry et al., 2001a). *Pax3* is known to be involved in the embryonic differentiation of Schwann cells from neural crest cells, and is expressed in non-myelinating Schwann cells during development. *Oct6/SCIP* is a marker for Schwann cell precursors in the promyelinating stage: its upregulation again indicates a reinduction of the developmental Schwann cell phenotype (Küry et al., 2001a; Scherer et al., 1994). Members of the *Hox* complex, *Hoxb5*, *Hoxd3* and *Hoxa6*, were reported to decline in Schwann cells after nerve crush (Küry et al., 2001a).

2.2. Dorsal root ganglion neurons change their expression profile

Sciatic nerve regeneration is accompanied by a variety of changes in the cell bodies of the dorsal root ganglion neurons: anatomical and morphological changes as well as changes in gene expression and cellular metabolism. The main morphological reaction of the cell body is ‘‘chromatolysis’’, the disintegration of rough endoplasmic reticulum, normally packed in large granular condensations. Furthermore, swelling of the cell body has been observed and the nucleus tends to move to the periphery of the cell body. Nuclear volume increases and nucleoli enlarge indicating that the response to injury is highly anabolic (Fawcett and Keynes, 1990; Lieberman, 1971).

Regeneration is associated with the expression of new genes and proteins (Aldskogius et al., 1992; Fawcett and Keynes, 1990; Fu and Gordon, 1997) (Fig. 1; Table 1). In general, transcription and translation of many proteins involved in neurite outgrowth during embryonic development are upregulated after nerve injury. The synthesis and axonal transport of cytoskeletal proteins such as actin, tubulin and peripherin are induced by axon injury (Aldskogius, 1992; Fawcett and Keynes, 1990), as well as the growth-associated protein B-50 (GAP-43) (Oestreicher et al., 1997; Plantinga et al., 1993; Van der Zee et al., 1989; Woolf et al., 1990) (Table 1). On the other hand, proteins that have in the adult organism a function in neurotransmitter release or more general, in the adult phenotype of the neurons, are downregulated. Examples are the neurotransmitters substance P (SP) and calcitonin gene-related peptide (CGRP), and neurofilament proteins, that are normally expressed only late in development, when the neuron has reached its target (Aldskogius et al., 1992; Fawcett and Keynes, 1990; Hökfelt et al., 1994).

The observation that genes expressed during embryonic dorsal root ganglion development are upregulated and genes involved in mature neuronal function are downregulated has lead to the hypothesis that, like Schwann cells, dorsal root ganglion neurons recapitulate developmental programs during regeneration (Fawcett and Keynes, 1990; Skene, 1989; Wong and Oblinger, 1990).

2.3. Expression alterations contradicting a recapitulation of development

Although at first sight, gene expression alterations in injured neurons seem to reflect developmental gene expression, when examined in more detail this is not always the case. In general, tubulin is upregulated, however, some of the developmentally expressed tubulin subclasses are not (Moskowitz et al., 1993). In line with this, the adult rather than the embryonic pattern of microtubule-associated proteins is retained (Fawcett et al., 1994; Ma et al., 2000). Schwann cells upregulate L1 and NCAM (Tacke and Martini, 1990), but dorsal root ganglion neurons do not, inducing close homologue of L1 (CHL1) instead, which is expressed predominantly during later stages of development (Zhang et al., 2000). These findings indicate that genes involved in outgrowth and pathfinding during development are not always involved in these processes during regeneration.

Table 1
Regeneration-associated alterations in gene expression in specific cell types after injury of the sciatic nerve

Genes	Up	Down	Cell types	References
Cytoskeletal (-associated) proteins				
Actin	x		SN	Nielsch and Keen, 1988
Beta-tubulin, type II, III	x		SN	Hoffman and Cleveland, 1988; Oblinger et al., 1989; Muma et al., 1990; Jiang et al., 1994; Moskowitz et al., 1993; Moskowitz and Oblinger, 1995; Hoffman and Luduena, 1996
Alpha-tubulin, type I	x		SN	Miller et al., 1989
Neurofilament H, M and L		x	SN	Hoffman and Cleveland, 1988; Oblinger et al., 1989; Muma et al., 1990; Jiang et al., 1994
Vimentin	x		SC	Neuberger and Cornbrooks, 1989
GFAP	x	x	SC	Neuberger and Cornbrooks, 1989; Quattrini et al., 1996, conflicting
C4		x	SC	Neuberger and Cornbrooks, 1989
S-100		x	SC	Neuberger and Cornbrooks, 1989
B-50/GAP-43	x		SN, SC	Van der Zee et al., 1989; Plantinga et al., 1993
Peripherin	x		SN	Wong and Oblinger, 1990
High molecular weight Tau		x, –	SN	Oblinger et al., 1991; Nothias et al., 1995, conflicting
Gelsolin	x		SC	Tanaka and Sobue, 1994
Beta-actin	x		SN	Lund and McQuarrie, 1996
KIF1A/1B/3A/3B/5		x	SN	Takemura et al., 1996
Microtubule-associated protein 1B (MAP1B)	x	P	SN, SC	Ma et al., 2000
MAP1B phosporylation mode I	x		SN, SC	Bush et al., 1996; Ramon-Cueto and Avila, 1999
MAP1B phosporylation mode II		x	SN, SC	Bush et al., 1996; Ramon-Cueto and Avila, 1999
Neurofilament M and L	x		SC	Fabrizi et al., 1997
SCG10 and CAP23	x		SN	Mason et al., 2002
Small proline-rich repeat protein 1A and S100C	x		SN	Bonilla et al., 2002
Caveolin-1		x	SC	Mikol et al., 2002
SNAP-25A		x	SN	Costigan et al., 2002; Xiao et al., 2002
Extracellular matrix proteins and receptors				
J1/Tenascin	x		F, SC	Martini et al., 1990
Collagen, type I, III, IV	x		F	Siironen et al., 1992a,b; Nath et al., 1997
Laminin beta1	x		F	Siironen et al., 1992b
Beta 4 integrin	x		SC	Quattrini et al., 1996
Beta 1 integrin	x		F	Taskinen et al., 1995
Laminin beta2	x		SN, SC, sat	Le Beau et al., 1995
F-spondin	x		#	Burstyn-Cohen et al., 1998
P200	x		SC	Chernousov et al., 1999
Fibronectin splice variants	x		SC	Vogelezang et al., 1999
Thrombospondin	x		SC	Hoffman and O'Shea, 1999
Beta-dystroglycan		x	SC	Masaki et al., 2000
Laminin-alpha2		x	SC	Masaki et al., 2000
Laminin-2 ($\alpha2\beta1\gamma1$) and -8 ($\alpha4\beta1\gamma1$)	x		#	Wallquist et al., 2002
Cell adhesion molecules				
NCAM and L1	x		SC	Martini and Schachner, 1988; Tacke and Martini, 1993
E-cadherin[a]	x	x	SC	Hasegawa et al., 1996; Tada et al., 2001[a]
Ninjurin2	x		SC	Araki and Milbrandt, 2000
Close homologue of L1 (CHL1)	x		SN	Zhang et al., 2000
Attractants, repellents and receptors				
Netrin-1	x		SC	Madison et al., 2000
Neuropilin-1	x		SN	Gavazzi et al., 2000, conflicting with Pasterkamp et al., 1998
Growth factors and receptors				
Nerve growth factor	x		SC, sat	Heumann et al., 1987; Meyer et al., 1992; Sebert and Shooter, 1993; Lee et al., 1998
High-affinity NGF receptor TrkA		x	SN	Verge et al., 1989, 1996; Mohiuddin et al., 1999
Brain-derived neurotrophic factor	x		SC	Meyer et al., 1992; Funakoshi et al., 1993; Sebert and Shooter, 1993
Low-affinity neurotrophin receptor p75	x		SC	Bolin and Shooter, 1993; Zhou et al., 1996; Akassoglou et al., 2002
Neurotrophin-3 (NT-3)		x	SC	Funakoshi et al., 1993; Cai et al., 1998
Neurotrophin-4 (NT-4)	x		SC	Funakoshi et al., 1993
High-affinity BDNF receptor TrkB (truncated)		x	SC	Funakoshi et al., 1993
High affinity NT-3 receptor TrkC (truncated)		x	SC	Funakoshi et al., 1993

(continued on next page)

Table 1 (*continued*)

Genes	Up	Down	Cell types	References
Growth factors and receptors				
High-affinity BDNF receptor TrkB (full length)	x		SN	Foster et al., 1994, immunoreactivity, conflicting with studies on mRNA
Low-affinity neurotrophin receptor p75		x	SN	Zhou et al., 1996
Other growth factors, cytokines and receptors				
Epidermal growth factor receptor (EGFR)	x		F, SC	Toma et al., 1992
Tissue plasminogen activator (tPA)		x	SC	Neuberger and Cornbrooks, 1989
Ciliary neurotrophic factor (CNTF)		x	SC	Rabinovsky et al., 1992; Friedman et al., 1992; Smith et al., 1993; Lee et al., 1995
Transforming growth factor (TFG)-β1	x		SC, mϕ	Rufer et al., 1994; La Fleur et al., 1996; Ryoke et al., 2000
Leukemia inhibitory factor (LIF)	x		SC	Curtis et al., 1994; Dowsing et al., 1999
Basic fibroblast growth factor (bFGF)	x		SN, SC, sat	Ji et al., 1995; Meisinger and Grothe, 1997
Glial cell line-derived neurotrophic factor (GDNF)	x		SC	Trupp et al., 1995; Naveilhan et al., 1997; Höke et al., 2002
Interleukin-6 (IL-6)	x		SC, SN	Bolin et al., 1995; Murphy et al., 1997
Insulin-like growth factor I (IGF-I)	x		SC, mϕ	Pu et al., 1995; Cheng et al., 1996
Insulin-like growth factor II (IGF-II)	x		SC	Pu et al., 1995
IGF binding protein 5 (IGFBP5)	x		SC	Cheng et al., 1996
Tumor necrosis factor (TNF) alpha	x		SC, mϕ	La Fleur et al., 1996; Shamash et al., 2002
Neuregulin	x		SC	Carroll et al., 1997
Neuregulin receptors, ErbB2, ErbB3	x, P		SC	Carroll et al., 1997; Kwon et al., 1997
GDNF receptor (GDNFR) alpha	x		SC	Naveilhan et al., 1997
Ret	x		SN	Naveilhan et al., 1997
Reg2	x		SN	Livesey et al., 1997; Averill et al., 2002
Monocyte chemoattractant protein-1 (MCP-1)	x		SC, en	Toews et al., 1998; Carroll and Frohnert, 1998; Taskinen and Roytta, 2000
Transforming growth factor (TGF)-α	x		sat	Xian and Zhou, 1999

Table 1 (*continued*)

Genes	Up	Down	Cell types	References
Other growth factors, cytokines and receptors				
Epidermal growth factor receptor (EGFR)	x		SN	Xian and Zhou, 1999
Macrophage migration inhibitory factor (MIF)	x		SN, SC, F, en	Nishio et al., 1999; Taskinen and Roytta, 2000
LIF receptor subunit beta and glycoprotein 130	x		SC	Dowsing et al., 1999
GDNF receptor (GFR) alpha-1 and -3	x		SN	Bennett et al., 2000; Höke et al., 2002
GFR alpha-2	x	x	SN	Bennett et al., 2000; Höke et al., 2002, conflicting
Interleukin (IL)-1 beta	x		#	Ryoke et al., 2000
RANTES	x		en, F, mϕ	Taskinen and Roytta, 2000
IL-11 and oncostatin	x		#	Ito et al., 2000
IL-11 receptor alpha		x	#	Ito et al., 2000
IL-18	x		mϕ	Menge et al., 2001
Fibroblast growth factor (FGF) receptor 3	x		SN	Grothe et al., 2001
Fibroblast growth factor (FGF)-5	x		SC	Scarlato et al., 2001
Tranforming growth factor (TFG)-beta2	x		SN	Stark et al., 2001
Platelet-derived growth factor (PDGF)-B chain[b]	x	x	SC	Oya et al., 2002
Osteopontin	x		SC	Jander et al., 2002
IL-1 alpha and beta	x		SC	Shamash et al., 2002
Neurotransmitters, peptides and receptors				
Cholecystokinin (CCK) and somatostatin (SOM)		x	SN	Shehab and Atkinson, 1986
Vasoactive intestinal polypeptide	x		SN	Shehab and Atkinson, 1986; Villar et al., 1989
Galanin	x		SN	Villar et al., 1989; Xu et al., 1990
Preprotachykinin (ppta)[c]/substance P (SP)	x	x	SN	Villar et al., 1989; Henken et al., 1990; Noguchi et al., 1994[c]
Neuropeptide Y (NPY)	x		SN	Wakisaka et al., 1991

Table 1 (*continued*)

Genes	Up	Down	Cell types	References
Neurotransmitters, peptides and receptors				
Neuronal nitric oxide synthase (nNOS)	x		SN	Fiallos-Estrada et al., 1993; Gonzalez-Hernandez and Rustioni, 1999a,b
Calcitonin gene-related peptide (CGRP)		x	SN	Hökfelt et al., 1994; Groves et al., 1996
Peripheral benzodiazepine receptor (PBR)	x		SC, mϕ, SN	Lacor et al., 1996, 1999; Xiao et al., 2002
Octadecaneuropeptide (ODN)	x		SC	Lacor et al., 1996
Islet amyloid polypeptide (IAPP)		x	SN	Mulder et al., 1997
Serotonin receptors		x	SC, SN	Yoder et al., 2002; Costigan et al., 2002
Alpha2A adrenergic receptor	x		SN	Birder and Perl, 1999
Purine receptor P2X3		x	SN	Bradbury et al., 1998
Angiotensin receptor 1b and 2	x		SN, SC	Gallinat et al., 1998
Angiotensin receptor 1a	x		SC	Gallinat et al., 1998
Endothelial nitric oxide synthase (eNOS)	x		en	Gonzalez-Hernandez and Rustioni, 1999a,b
Inducible nitric oxide synthase (iNOS)	x		mϕ	Gonzalez-Hernandez and Rustioni, 1999a,b
Bradykinin B2 receptor	x		SN	Lee et al., 2002
Purine receptor P2Y1	x		SN	Xiao et al., 2002
Nicotinic acetylcholine receptor a7 subunit	x		SN	Xiao et al., 2002
$GABA_A$ receptor α5 subunit	x		SN	Xiao et al., 2002
Bradikinin B2 receptor	x		SN	Lee et al., 2002
Transcription factors				
Jun	x		SN	Leah et al., 1991; Fiallos-Estrada et al., 1993; Jenkins et al., 1993; Soares et al., 2001
Suppressed cAMP-inducible POU (SCIP)	x		SC	Scherer et al., 1994; Gondré et al., 1998
Oct2	x		SN	Begbie et al., 1996
Brn3a		x	SN	Begbie et al., 1996
Isl1		x	SN	Hol et al., 1999
ATF3	x		SN	Tsujino et al., 2000
Mash2	x		SC	Küry et al., 2001a

Table 1 (*continued*)

Genes	Up	Down	Cell types	References
Transcription factors				
Hoxb5, *Hoxd3*, *Hoxa6*		x	SC	Küry et al., 2001a
STAT3	P		SC	Sheu et al., 2000
Sharp2 and hairy/enhancer of split (HES) 1		x	SN	Kabos et al., 2002
Hormones and receptors				
Nuclear thyroid hormone receptors	x		SC	Barakat-Walter et al., 1993; Glauser and Barakat-Walter, 1997
3 Beta-hydoxysteroid dehydrogenase		x	SC	Robert et al., 2001; Schumacher et al., 2001
Type 2 and 3 deiodinase	x		F	Li et al., 2001a,b
Kinases, phosphatases and signal transduction				
Protein-tyrosine kinase pp60c-src and targets	x, P		SC, SN	Le Beau et al., 1991; Ignelzi et al., 1992
Mitogen-activated protein kinase (MAP-K)	x		SC, SN	Svensson et al., 1995; Kim et al., 2002
cAMP phosphodiesterase	x, A		SC	Walikonis and Poduslo, 1998
Adenylyl cyclase		A	SC	Walikonis and Poduslo, 1998
Protein tyrosine phosphatase (PTP) alpha		x	SN	Haworth et al., 1998
Protein tyrosine phosphatase (PTP) sigma	x		SN	Haworth et al., 1998
Leukocyte common antigen-related protein tyrosine phosphatase receptor (LAR)		x	SN	Haworth et al., 1998; Xie et al., 2001
ERK1/2	P		SC	Sheu et al., 2000; Abe et al., 2001; Akassoglou et al., 2002
Channels/transmembrane proteins				
Potassium channels, MK1 and MK2		x	SC	Chiu et al., 1994
Connexin32		x	SC	Chandross et al., 1996; Nagaoka et al., 1999
Connexin43 and -46	x		F, SC	Chandross et al., 1996; Nagaoka et al., 1999
Alpha2 and Beta2 subunits of Na+, K+-ATPase	x, A		SC	Kawai et al., 1997
Connexin26[b]	x	x		Nagaoka et al., 1999
L-Calcium channel α2δ1	x		SN	Xiao et al., 2002

(*continued on next page*)

Table 1 (*continued*)

Genes	Up	Down	Cell types	References
Channels/transmembrane proteins				
Sodium channel β2	x		SN	Xiao et al., 2002
Calcium channel a2 subunit	x		SN	Costigan et al., 2002
Proteases and protease regulators				
Glial-derived nexin	x		SC	Meier et al., 1989
Endopeptidase-24.11		x	SC	Kioussi et al., 1995
Matrix metalloproteinases (MMP) -2, -3 and -9	x		SC, mϕ	La Fleur et al., 1996; Ferguson and Muir, 2000
Tissue inhibitor of MMPs (TIMP-1)	x		SC, mϕ	La Fleur et al., 1996
Cellular metalloprotease disintegrin (rMDC15)	x		SC, SN	Bosse et al., 2000
Plasminogen activators	x		SN	Siconolfi and Seeds, 2001
Damage-induced neuronal endopeptidase (DINE)	x		SN	Kato et al., 2002
Myelin genes				
P0		x	SC	LeBlanc and Poduslo, 1990; Mitchell et al., 1990; Gupta et al., 1993
MBPs		x	SC	LeBlanc and Poduslo, 1990; Mitchell et al., 1990; Gupta et al., 1993
MAG		x	SC	LeBlanc and Poduslo, 1990; Mitchell et al., 1990; Gupta et al., 1993
P2		x	SC	LeBlanc and Poduslo, 1990
Plasmolipin		x	SC	Gillen et al., 1996
Miscellaneous enzymes				
Aldose reductase		x, A	SC	Wong et al., 1992
2′,3′ -Cyclic nucleotide 3’-phosphodiesterase		x	SC	LeBlanc et al., 1992
NADPH-diaphorase	x, A		SN	Fiallos-Estrada et al., 1993
Beta-1, 4-galactosyltransferase II and V	x		SC	Shen et al., 2002
GTP cyclohydrolase	x		SN	Costigan et al., 2002
Miscellaneous genes				
Apolipoprotein E	x		#	LeBlanc and Poduslo, 1990
Apolipoprotein D	x		F	Spreyer et al., 1990
Beta-amyloid precursor protein (APP)	x		SN	Scott, 1992
Hemopexin	x		SC, F, mϕ	Swerts et al., 1992; Camborieux et al., 1998; Madore et al., 1999

Table 1 (*continued*)

Genes	Up	Down	Cell types	References
Miscellaneous genes				
PMP22		x	SC	Kuhn et al., 1993
FKBP-12	x		SN	Lyons et al., 1995
Lactoseries oligosaccharides		x	SN	Groves et al., 1996
4C5	x		SC	Thomaidou et al., 1996
Clusterin (C4)	x		#	Bonnard et al., 1997
Cyclin D1	x		SC	Atanasoski et al., 2001
Heat shock protein (Hsp) 27	x, P		SN	Benn et al., 2002
Immediate–early serum-responsive JE	x		SN	Costigan et al., 2002
Nerve growth factor-inducible protein (VGF)	x		SN	Costigan et al., 2002

Genes are classified according to their function and ordered chronologically according to their year of publication. Only the genes expressed in dorsal root ganglia and sciatic nerve cells are shown; the spinal cord motor neurons are left aside. The types of injury are also not considered, assuming that similar gene expression changes occur after crush lesion, transection, ligation or other types of injury to the nerve fibers. Most of the changes shown here are based upon mRNA studies; some are based on immunocytochemical studies, or on phosphorylation (P) or activity (A) measurements. Finally, studies using microarrays or differential display were not included in this table unless the cell types in which gene expression alterations occurred were checked. For detailed information from gene expression profiling studies, see Bosse et al. (2001), Costigan et al. (2002) and Xiao et al. (2002).

SN = DRG neurons; SC = Schwann cells; sat = satellite cells; mϕ = macrophages; en = endothelial cells; F = fibroblasts; # = sciatic nerve, cell type not specified.

If conflicting data exist, these are indicated in the references column.

[a] Dual regulation: first down- then upregulated.

[b] Dual regulation: first up- then downregulated.

[c] Dual response: upregulation in small SN, downregulation in large SN.

Similarly, the involvement of neurotrophins seems not to fully recapitulate development. Neurotrophins are known to be important attractants and survival factors for dorsal root ganglion neurons during development, and exogenous application of neurotrophins during regeneration have beneficial effects (Lewin et al., 1997; Mohiuddin et al., 1999; Raivich and Kreutzberg, 1993). However, their high-affinity (Trk) receptors are not upregulated after injury; TrkA is even downregulated (Mohiuddin et al., 1999; Raivich and Kreutzberg, 1993; Verge et al., 1989). Many other (neurotrophic) growth factors are also involved in regeneration, like glial cell line-derived neurotrophic factor (GDNF) (Bennett et al., 2000), neuroactive cytokines (reviewed in Murphy et al., 1997; Unsicker et al., 1992), fibroblast growth factor (FGF) (Grothe et al., 2001; Grothe and Nikkhah, 2001; Ji et al., 1995), insulin-like growth factor (IGF) (Craner et al., 2002; Pu et al., 1995; Raivich and Kreutzberg, 1993) and transforming growth factor (TGF) (Xian and Zhou, 1999). Some of these growth factors have known roles in dorsal root ganglion development, others do not. Moreover, there are now many examples of genes not (reported to be) expressed in developing dorsal root ganglia,

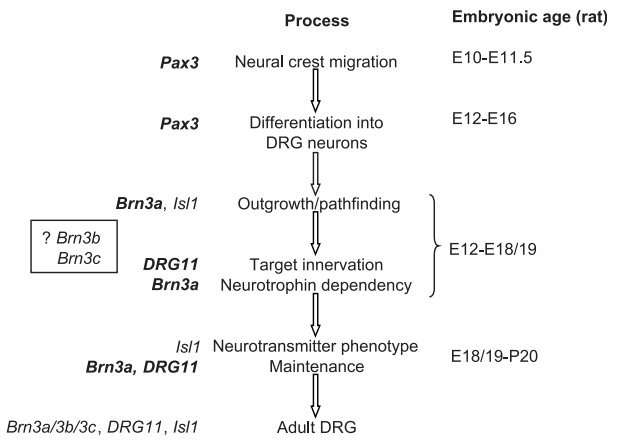

Fig. 2. Expression of homeobox genes during successive stages of dorsal root ganglion (DRG) development. Homeobox genes that have a known function in a certain process in the development of dorsal root ganglion neurons are typed in bold face. These include *Pax3*, involved in neural crest migration and differentiation of dorsal root ganglion neurons (Koblar et al., 1999), *Brn3*a, essential for neurite outgrowth, expression of neurotrophin receptors and neuronal survival (maintenance) (Eng et al., 2001), and *DRG11*, involved in central target innervation and neuronal maintenance (Chen et al., 2001). The functions of *Isl1* in dorsal root ganglion development are largely unknown, but in other types of neurons it is involved in outgrowth and neurotransmitter phenotype (Hol et al., 1999; Thor et al., 1991). *Brn3b* and *-3c* are expressed in developing dorsal root ganglion, but their functions in dorsal root ganglion development are unclear (Erkman et al., 1996; Gan et al., 1996). Finally, adult dorsal root ganglion neurons express *Brn3a*, *-3b*, *-3c*, *DRG11* and *Isl1*, but their functions in the adult dorsal root ganglia are unknown.

3.1.2. Paired and paired-like homeobox genes

The paired homeobox gene *Pax3* is important during early dorsal root ganglion development. The *Pax3* null mutant, called *Splotch*, is defective in neural tube closure and crest cell emigration. Pigment cells, sympathetic and dorsal root ganglia, enteric neurons and cardiac structures are absent or severely reduced in this null mutant. The defect in emigration is thought to be due to the lack of interaction between crest cells and the somites (Anderson, 1999; Le Douarin and Kalcheim, 1999; Chalepakis et al., 1993). *Pax3* also involved in the generation of dorsal root ganglion neurons themselves. Koblar et al. (1999) showed a fivefold reduction in the ability of *Splotch* neural crest cells to generate dorsal root ganglion neurons in vitro. In cultured dorsal root ganglia *Pax3* antisense oligonucleotides resulted in a 90% inhibition of production of new sensory neurons (Koblar et al., 1999).

The paired-like homeobox gene *DRG11* was found in dorsal root ganglia by Saito et al. (1995) using reverse transcriptase polymerase chain reaction (RT-PCR). *DRG11* is specifically expressed in dorsal root ganglion neurons and in the dorsal horn of the spinal cord, where interneurons are located which receive synaptic input from the dorsal root ganglion (Akopian et al., 1996; Saito et al., 1995). *DRG11* was hypothesized to play a role in specification of the neurotransmitter phenotype of dorsal root ganglion neurons or in synapse formation. The *DRG11* knock-out mouse, generated by Chen et al. (2001), displays abnormalities in innervation of the lateral dorsal horn by dorsal root ganglion neurons innervating the skin. Although at embryonic stages, no significant dorsal root ganglion cell loss is found, in adult mice, almost 30% of the dorsal root ganglion neurons are lost. The knock-out mice display abnormalities in pain sensitivity. These data suggest that *DRG11* is required for the projections of nociceptive neurons to the spinal cord and for maintenance of dorsal root ganglion neurons in adult dorsal root ganglia (Chen et al., 2001). The peripheral connectivity of dorsal root ganglion neurons in these mice has not yet been assessed, but in view of the phenotype may be affected as well (Patapoutian, 2001).

3.1.3. LIM homeobox genes

The LIM homeobox gene *Isl1* is expressed in adult dorsal root ganglia, in a subset of neurons. The function of *Isl1* in developing dorsal root ganglia, to date, is not known, although it is abundantly expressed in many dorsal root ganglion neurons during development. In the spinal cord, *Isl1* importantly contributes to the combinatorial genetic network that controls motor neuron development (Shirasaki and Pfaff, 2002; Tanabe and Jessell, 1996). Moreover, it has been indicated that *Isl1* is involved in outgrowth, pathfinding and neuroendocrine phenotypes of neurons (Thor et al., 1991; Thor and Thomas, 1997).

3.2. Homeobox genes in dorsal root ganglion neuron regeneration

In this section, studies aimed to determine the expression of homeobox genes in regenerating dorsal root ganglion neurons will be summarized. As described above, several homeobox genes are known to be expressed in the adult dorsal root ganglion. Recently, we performed a screen for expressed homeobox genes based on a degenerate PCR strategy. We identified 22 genes expressed in uninjured dorsal root ganglion neurons (Table 2) (Vogelaar et al., 2003). The homeobox genes *Brn3a*, *Isl1* and *Oct2* have been shown before to undergo changes after sciatic nerve injury. Here, we will discuss these alterations and our own observations on the expression levels of some more homeobox genes in view of the question whether the molecular mechanisms of regeneration recapitulate development.

3.2.1. Brn3a and Oct2

Due to its prominent role in developmental outgrowth and survival of dorsal root ganglion neurons, *Brn3a* is a likely candidate for a role in regeneration. Both during development and in the adult it is expressed in most dorsal root ganglion neurons (Xiang et al., 1995). After sciatic nerve injury, however, *Brn3a* was reported to be down-regulated (Begbie et al., 1996; Küry et al., 2001a), suggesting that *Brn3a* does not have the same function in regenerating and developing dorsal root ganglia. Indeed,

Table 2
The homeobox genes expressed in adult rat dorsal root ganglia

No.	Homeobox gene	Homeobox class	Genbank accession no.
HD PCR			
1	*DRG11*	paired-like	U29174
2	*Gbx2*	GBX class	AF390072[a]
3	*Gsc*	paired-like	AY169318[a]
4	*Gsh4*	LIM	S71659
5	*Hoxa1*	Hox complex	U93092
6	*Hoxc5*	Hox complex	U28071
7	*Lmx1b*	LIM	AF390073[a]
8	*Msx1*	Msx family	D83036
9	*Msx3-like*	Msx family	AF390078[a]
10	*Otp*	paired-like	J10413
11	*Pax3*	paired	AF390074[a]
12	*Prx2*	paired-like	X52875
13	*Prx3*	paired-like	AJ002258
14	*Ptx2*	paired-like	AF039832
15	*Vsx2-like*	paired-like	AF390079[a]
16	*Zfh4*	zinc finger-HD	L36173
POU PCR			
17	*Brn2*	POU	L27663
18	*Brn3a*	POU	AF390075[a]
19	*Brn3*	POU	AF390076[a]
20	*Brn4/RHS2*	POU	Z11834
21	*Oct1*	POU	U17013
22	*Oct6*	POU	NM_011141

The homeobox genes were identified using RT-PCR on mRNA from DRG L4–L6. The homeobox gene classes to which they belong and the Genbank accession numbers are shown in the right columns. Accession numbers marked with [a] represent newly submitted sequences (Vogelaar et al., 2003).

Brn3a has been implicated in the expression of neurotrophin receptors in embryonic dorsal root ganglion neurons, whereas in adult dorsal root ganglion neurons, neurotrophin receptors are either unchanged or downregulated (Mohiuddin et al., 1999; Raivich and Kreutzberg, 1993; Verge et al., 1989). We speculate that the downregulation of *Brn3a* may be causative for the downregulation of *TrkA*.

Another POU homeobox gene studied by Begbie et al. (1996) was *Oct2*. This gene was reported to be slightly upregulated after crush, which could reflect both adult and embryonic mechanisms, as it is highly expressed in both embryonic and adult dorsal root ganglia (Begbie et al., 1996).

3.2.2. Isl1

Hol et al. (1999) showed a slight downregulation of *Isl1* 7 days after sciatic nerve crush. With quantitative PCR, we detected a 2.8-fold decrease in *Isl1* expression levels at 1 day after crush, indicating a transient effect of the crush lesion on the expression of this homeobox gene (Vogelaar et al., submitted). The weaker downregulation reported by Hol et al. may reflect a fast return of *Isl1* expression to normal levels, which is in accord with our findings. Since *Isl1* is expressed at high levels in many neurons during dorsal root ganglion development, and in a restricted neuronal subpopulation in adult and regenerating dorsal root ganglia (Hol et al., 1999), it was concluded that embryonic *Isl1* expression patterns were not recapitulated during regeneration. Therefore, a role for *Isl1* in outgrowth and pathfinding of regenerating neurons seems unlikely. The downregulation of *Isl1* may be correlated with the downregulation of the neurotransmitter phenotype since *Isl1* has been implicated in the neuroendocrine phenotype of cells (Thor et al., 1991).

3.2.3. No alterations in Pax3, DRG11 and Lmx1b expression levels

The above-described role for *Pax3* in both dorsal root ganglion neuron and Schwann cell differentiation, and its upregulation in distal Schwann cells, prompted us to quantify *Pax3* in regenerating dorsal root ganglia. As basal levels were extremely low, damaged dorsal root ganglion neurons (like Schwann cells) reexpress *Pax3*. Quantification of *Pax3*, however, showed no change in the levels of this homeobox gene (Vogelaar et al., submitted). This observation is underscored by data on *NCAM*, a downstream target gene of *Pax3*. In Schwann cells, *NCAM* is upregulated, whereas in neurons, it is not (Tacke and Martini, 1990; Zhang et al., 2000). This again points to a difference in gene expression between developing and regenerating dorsal root ganglion neurons.

DRG11 is among the most abundantly expressed homeobox genes in adult dorsal root ganglia. In the adult, it is restricted to a subpopulation of—probably nociceptive—neurons, whereas it is expressed in many dorsal root ganglion neurons in the embryo (Chen et al., 2001; Saito et al., 1995; Vogelaar et al., 2003). Its role in embryonic (central) target innervation and adult cell survival (Chen et al., 2001) would suggest that an upregulation was to be expected if developmental expression would have been recapitulated. However, we did not find a difference in expression levels of this homeobox gene (Vogelaar et al., submitted).

Finally, the expression levels of *Lmx1b*, a homeobox gene that is expressed in the adult but not in the embryonic dorsal root ganglia (Asbreuk et al., 2002; Vogelaar et al., 2003) were also not altered (Vogelaar et al., submitted). A recapitulation of development would be reflected by a decreased expression of this gene.

3.2.4. Regeneration-specific mechanisms

From the lack of a recapitulation of developmental homeobox gene expression, it follows that the transcriptional mechanisms for dorsal root ganglion neuron differentiation, outgrowth, pathfinding and survival are different between regenerating and developing dorsal root ganglion neurons. This indicates that, in contrast to Schwann cells, the reaction of dorsal root ganglion neurons to injury is not simply a dedifferentiation followed by redifferentiation. The phenotype adopted by the injured neurons to initiate regeneration, therefore, is not an embryonic phenotype, but reflects adult mechanisms for outgrowth and pathfinding. This can be considered as a regeneration-specific mecha-

nism reflected by specific changes in gene expression, summarized in Table 1. This may not be surprising since the cellular environment and the connectivity of the neurons is profoundly different in the adult versus the embryo. Dorsal root ganglion neurons develop in the vicinity of their developing targets, i.e., dermamyotome, which develops from differentiating somites. Thus, the distance traveled and the access to target-derived factors are dramatically different between development and regeneration. The axonal environment is also fundamentally different due to cytokines produced by invading macrophages and Schwann cells (Table 1). The way external signaling molecules participate in the response of injured dorsal root ganglion neurons may be an important aspect of the regeneration-specific mechanism. In the following section, signaling and transcription processes relevant for the molecular mechanisms of regeneration will be addressed.

4. Signaling molecules used by regenerating dorsal root ganglion neurons

The mechanisms underlying regenerative growth are likely to involve neurotrophic factors. The decrease in availability of NGF, due to the disruption of the nerve fibers and the decrease in the rate of retrograde transport (Lee et al., 1998; Raivich and Kreutzberg, 1993), is generally regarded as the main trigger for the response of dorsal root ganglion neurons to injury (Aldskogius et al., 1992; Fawcett and Keynes, 1990; Verge et al., 1996). This is supported by Shadiack et al. (2001) showing induction of axotomy-like changes in neuropeptide expression in dorsal root ganglion neurons after the application of NGF antiserum. It seems likely that the upregulation of neurotrophins by Schwann cells and satellite cells (Table 1) observed after injury play important roles in the mechanisms underlying regeneration. However, the Trk receptors (*TrkA*, *-B* and *-C*) in dorsal root ganglion neurons are not induced. *TrkA* is even downregulated, indicating that developmental Trk expression patterns are not recapitulated (Table 1). Moreover, the signal transduction pathways used by dorsal root ganglion neurons during development and regeneration have been recently been reported to be different. Extracellular signal-related kinase (ERK) and phosphatidylinositol-3 kinase (PI3-K), the major signal transduction pathways activated by the Trk receptors (for a review, see Kaplan and Miller, 2000), were shown to be involved in axonal outgrowth from embryonic dorsal root ganglia, but not from lesioned dorsal root ganglia (Liu and Snider, 2001). ERK phosphorylation after injury has been reported in Schwann cells, but not in dorsal root ganglion neurons (Abe et al., 2001; Sheu et al., 2000).

If neurotrophins are not directly involved in regenerative outgrowth, what proteins then are? Although their role in inflammatory responses is well known, cytokines also have effects on the nervous system. The so-called neuroactive cytokines include ciliary neurotrophic factor (CNTF), leukemia inhibitory factor (LIF), interleukin-6, FGF and TGF (Gadient and Otten, 1997; Grothe and Nikkhah, 2001; Murphy et al., 1997, Unsicker et al., 1992). Of these, only *CNTF* expression has been reported to decrease after nerve injury, the others are all upregulated (Table 1) (for reviews, see Murphy et al., 1997; Markus et al., 2002). Neuroactive cytokines signal through gp130 receptors upstream of signaling molecules like JAK2 and STAT3. In contrast to the apparent disuse of neurotrophin signaling in regenerative outgrowth, Liu and Snider (2001) observed that JAK2 and STAT3 are involved in regenerative outgrowth from lesioned dorsal root ganglia, but have no effect on embryonic dorsal root ganglia. Moreover, the transcription factor STAT3 is phosphorylated in dorsal root ganglion neurons after nerve injury (Liu and Snider, 2001). These data indicate that cytokines may be important in controlling regeneration-associated gene expression in dorsal root ganglion neurons through the JAK/STAT signal transduction pathway (Markus et al., 2002). In line with this, genes known to be induced by LIF and interleukin-6—*galanin*, *peripherin* and *Reg-2* (Cafferty et al., 2001; Livesey et al., 1997)—are upregulated in dorsal root ganglion neurons (Table 1) (Averill et al., 2002; Villar et al., 1989; Wong and Oblinger, 1990). Genes known to be induced by NGF, among others *SP* and *CGRP* (Lindsay and Harmar, 1989; Mohiuddin et al., 1999; Verge et al., 1995), are downregulated in response to nerve injury (Table 1) (Henken et al., 1990; Hökfelt et al., 1994; Villar et al., 1989). Moreover, *LIF* null mutant mice have no phenotype in the development of dorsal root ganglion neurons, but in the adult null mutants sciatic nerve regeneration is impaired and small peptidergic neurons die after injury (Cafferty et al., 2001).

The mechanisms of cell survival may also differ between regenerating and developing neurons. The upregulation in dorsal root ganglion neurons of both neuroactive cytokines, like TGF-β and basic FGF, and their receptors suggest autocrine mechanisms for survival after injury. NGF and BDNF are also upregulated in dorsal root ganglion neurons after nerve injury (Sebert and Shooter, 1993) (also pointing to an autocrine loop), but as mentioned before, their receptors are not, again indicating a less important role for neurotrophins. The dependency for survival on target-derived neurotrophic support seems to be absent in adult and regenerating neurons (Lindsay, 1992).

These data corroborate the notion that the molecular mechanisms underlying gene expression alterations during regeneration are different from those used in development. Observations point to a regeneration-associated role of cytokines, rather than neurotrophins, in outgrowth and survival of dorsal root ganglion neurons (Fig. 3) (Markus et al., 2002). However, it is important to note that this does not rule out a function for neurotrophins in regeneration, but that it does contradict a direct effect of neurotrophins on dorsal root ganglion neurons. The enhanced production of endogenous neurotrophins by Schwann cells may not have direct effects on dorsal root ganglion neurons, but are

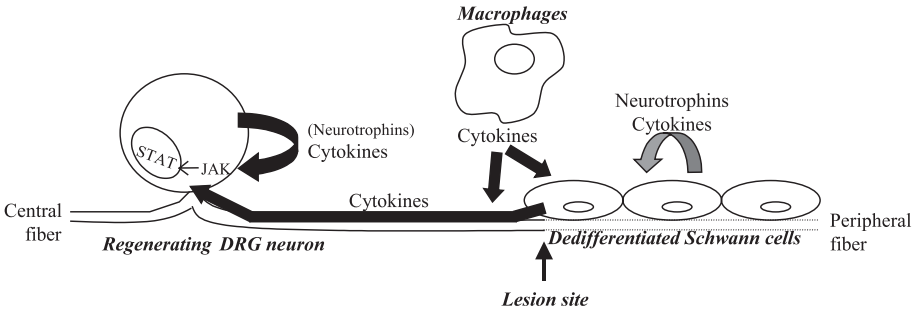

Fig. 3. Neurotrophic support of dorsal root ganglion (DRG) neurons and Schwann cells after sciatic nerve crush. Upon injury, dedifferentiated Schwann cells produce high amounts of neurotrophins and cytokines, the latter also produced by macrophages. Studies on signal transduction pathways revealed that the regenerating dorsal root ganglion neurons utilize neuroactive cytokines rather than neurotrophins for support of regenerative outgrowth (Liu and Snider, 2001; Markus et al., 2002). The cytokines are retrogradely transported to the cell body (Curtis et al., 1994) and signal via JAK to the transcription factor STAT3, thus influencing gene expression in the regenerating neurons (Cafferty et al., 2001; Liu and Snider, 2001). Neurotrophins seem to play only an indirect role in outgrowth and survival of the injured neurons via the support of Schwann cells in the distal sciatic nerve (Mohiuddin et al., 1999).

thought to indirectly stimulate regeneration through effects on Schwann cells (Mohiuddin et al., 1999) (Fig. 3).

5. Transcriptional mechanisms other than homeobox genes

The above-described differences in the signal transduction pathways utilized during regeneration and development are likely to result in different transcriptional regulation of genes. As shown before, homeobox gene expression patterns upon nerve crush contradict a recapitulation of development. Other transcription factors, too, point to a difference in gene regulation between embryonic and regenerating dorsal root ganglion neurons. The first transcription factor that has been shown to be upregulated in dorsal root ganglion neurons after nerve crush was c-jun (Table 1). Interestingly, c-Fos is not upregulated in dorsal root ganglion neurons (Leah et al., 1991; Plantinga et al., 1994; Soares et al., 2001). The increase in c-Jun is among the earliest reactions described and seems to coincide with the onset of the cell body response to injury. During development, subsets of dorsal root ganglion neurons show only moderate expression of c-Jun, retained at constitutively low levels in adulthood (Herdegen and Leah, 1998, and references therein). The upregulation of c-Jun in virtually all injured cells, therefore, does not reflect a recapitulation of development. c-Jun is known to be upstream of genes with activator protein-1 (AP-1) binding sites in their promoter, among which is *B-50* (De Groen et al., 1995). This finding marks *B-50* as an important target gene of c-Jun with respect to regeneration (Herdegen and Leah, 1998, and references therein). Udvadia et al. (2001) showed in the zebrafish that a 1-kb fragment of the *B-50* promoter of the rat, directing *B-50* expression during development, was not capable of reactivating *B-50* during regeneration. This indicates that, indeed, a different part of the *B-50* promoter is used during regenerative axon outgrowth as compared to development. These observations indicate that genes that are expresses in both developing and regenerating neurons are not necessarily regulated in the same manner.

Another transcription factor described in regeneration is activating transcription factor 3 (ATF3). ATF3 is closely related to c-jun and activates transcription as a heterodimer with c-jun. ATF3 mRNA is not expressed in embryonic or adult dorsal root ganglia, but is induced after nerve injury, mostly in the same cells that upregulated c-jun. In general, ATF3 expression is induced in many cell types in response to stress signals, indicating that its activation is not specific to nerve injury (Tsujino et al., 2000).

Finally, a recent report of Kabos et al. (2002) on basic helix–loop–helix transcription factors showed that Sharp2 (enhancer of split- and hairy-related protein 2) and HES1 (hairy enhancer of split), negative regulators of developmental neurite outgrowth, are downregulated in dorsal root ganglion neurons, but positive regulators, neurogenins, are not induced (Table 1).

6. Conclusions

Taken together, in this review, we have demonstrated that during regeneration of the crushed sciatic nerve, dorsal root ganglion neurons do not simply recapitulate the developmental expression patterns of homeobox genes that are functionally involved in the embryonic dorsal root ganglia in neuronal differentiation, axonal outgrowth, pathfinding and neuronal survival. The transcriptional regulation of these processes during regeneration is, therefore, fundamentally different from these during development. There is evidence that adult dorsal root ganglion neurons utilize neuroactive cytokines rather than neurotrophins for regenerative outgrowth and survival (Fig. 3). The preferential induction of target genes downstream of cytokine rather than neurotrophin signal transduction pathways underscores this notion. Transcription factors other than homeobox genes that are induced during regeneration also reflect a difference between regenerating and developing dorsal root ganglia.

We would like to propose that in the adult dorsal root ganglia, regeneration-specific mechanisms exist, inducing regeneration-specific gene expression in dorsal root ganglion neurons. These mechanisms may reflect adult gene regulation rather than developmentally controlled gene expression, and are partly imposed by the different context of adult versus embryonic dorsal root ganglion neurons and fibers. Differences in the neuronal environment implicate different signaling molecules and different signal transduction cascades. This leads to a different gene expression program in regenerating as opposed to developing dorsal root ganglion neurons. In future studies, further unraveling of the signal transduction pathways and the transcriptional regulation in regenerating dorsal root ganglion neurons should provide more insight into those mechanisms that are regeneration-specific. This may result in novel pharmacological strategies to promote the regeneration process.

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