Serum response factor mediated gene activity in physiological and pathological processes of neuronal motility

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INTRODUCTION

Serum response factor (SRF), a MADS box transcription factor (Norman et al., 1988), was originally identified as the gene regulator activated by serum stimulation of starved cells (Posern and Treisman, 2006; Miano et al., 2007; Olson and Nordheim, 2010). Serum response elements (SRE) recognized by SRF are present in a wealth of genes with diverse functions, yet are enriched in two classes of SRF target genes (Philippar et al., 2004; Selvaraj and Prywes, 2004; Sun et al., 2006; Stritt et al., 2009):

(i) Immediate-early genes (IEGs), including genes encoding transcription factors (Curran and Morgan, 1995; Herdegen and Leah, 1998), growth factors (e.g., Ctgf, Bdnf), and, e.g., the synaptic plasticity associated gene Arc (Arg3.1). IEG induction is a rapid – activated within minutes – but transient gene expression response, not requiring new protein synthesis.

(ii) Many genes encoding components of the actin cytoskeleton including actin isoforms (Actb, Acta, Actg, Acta) or ABPs (actin binding proteins; gelsolin, vinculin, transgelin, tropomyosin, myosins, vinculin) are transcriptionally regulated by SRF. Such a unique gene regulatory signature imposed by SRF toward actin cytoskeletal genes has not been described for non-neuronal cells (Miralles et al., 2003). MRTF-A’s function as a sensor of actin dynamics relies on its capability to bind monomeric actin and – at least in part – on shuttling in and out of the nucleus (Mouilleron et al., 2008).

Besides direct transcriptional regulation, SRF controls – via a post-translational mechanism – activity of the actin severing protein coflin (Alberti et al., 2005; Mokalled et al., 2010; see also Vartiainen et al., 2007). In un-stimulated cells, monomeric G-actin blocks MRTF-A’s ability to augment SRF’s transcriptional activity by (i) decreasing MRTF-A nuclear import, (ii) enhancing MRTF-A nuclear export in an actin-dependent manner, and (iii) by a nuclear G-actin fraction binding directly to MRTF-A (Vartiainen et al., 2007).

In recent years, the transcription factor serum response factor (SRF) was shown to contribute to various physiological processes linked to neuronal motility. The latter include cell migration, axon guidance, and, e.g., synapse function relying on cytoskeletal dynamics, neurite outgrowth, axonal and dendritic differentiation, growth cone motility, and neurite branching. SRF teams up with myocardin related transcription factors (MRTFs) and ternary complex factors (TCFs) to mediate cellular actin cytoskeletal dynamics and the immediate-early gene (IEG) response, a bona fide indicator of neuronal activation. Herein, I will discuss how SRF and cofactors might modulate physiological processes of neuronal motility. Further, potential mechanisms engaged by neurite growth promoting molecules and axon guidance cues to target SRF’s transcriptional machinery in physiological neuronal motility will be presented. Of note, altered cytoskeletal dynamics and rapid initiation of an IEG response are a hallmark of injured neurons in various neurological disorders. Thus, SRF and its MRTF and TCF cofactors might emerge as a novel trio modulating peripheral and central axon regeneration.

Keywords: SRF, TCF, MRTF, axon, regeneration, neurite, cytoskeleton, IEG
Upon cell stimulation, Rho-GTPases stimulate F-actin assembly and thereby a depletion of the G-actin pool. This liberates MRTF-A from G-actin and allows, e.g., for MRTF-A nuclear entry (Miralles et al., 2003). Notably, Rho-GTPases such as RhoA, Cdc42, and Rac1 are important actin cytoskeletal modulators of neuronal morphology and axonal regeneration (Tahirovic and Bradke, 2009; Hall and Lalli, 2010). Thus, SRF might be a signaling intermediate bridging the impact of Rho-GTPases on cytoskeletal dynamics. In sum, G-actin reduces, whereas F-actin assembly augments SRF-mediated gene activity (Posern et al., 2002, 2004; Posern and Treisman, 2006; Knoll and Nordheim, 2009; Stern et al., 2009; Knoll, 2010; Olson and Nordheim, 2010). This principal mechanism appears to be conserved also in neurons. However, in neurons modifications to this scheme might exist, as constitutive nuclear MRTF localization has been reported as well as MRTF shuttling (Tabuchi et al., 2005; Kalita et al., 2006; Wickramasinghe et al., 2008; Stern et al., 2009; Knoll, 2010).

Myocardin related transcription factors and TCFs may act antagonistically in some instances by competing for SRF occupancy as demonstrated in muscle cells (Wang et al., 2004). In addition, a cross-talk between the upstream pathways of MRTF and TCF activation has been shown. Here, nuclear MAL export is addition, a cross-talk between the upstream pathways of MRTF antagonistically in some instances by competing for SRF occupancy as demonstrated in muscle cells (Wang et al., 2004). In addition, a cross-talk between the upstream pathways of MRTF and TCF activation has been shown. Here, nuclear MAL export is facilitated by the availability of Mig6;Descot et al., 2009) kinase signaling via regulation of the mitogen-inducible gene 6 (Mig6; Descot et al., 2009).

**SRF and its Co-factors in Physiological Processes Requiring Neuronal Motility**

**SRF Functions in Neuronal Motility**

Up until now, the role of SRF in neuronal motility processes has been investigated in greater detail than its TCF and MRTF cofactors.

The elucidation of SRF functions in neurons has been greatly aided by the availability of Srf mouse mutants (Wiebel et al., 2002; Alberti et al., 2005). Conditional Srf ablation, e.g., in the murine forebrain revealed a wealth of neuronal motility phenotypes (Knoll and Nordheim, 2009).

In early postnatal stages, SRF ablation resulted in impaired tangential cell migration along the rostral migratory stream (Alberti et al., 2005). Besides cell migration, neurite outgrowth, axon vs. dendrite differentiation, and axon guidance of hippocampal and sensory axons were disturbed in Srf mutants (Knoll et al., 2006; Wickramasinghe et al., 2008; Stern et al., 2009). In the hippocampus of SRF-deficient mice, mossy fiber axon guidance was impaired (Knoll et al., 2006). SRF-deficient neurons are frequently bipolar in shape and reduced in neurite length (Knoll et al., 2006; Stern et al., 2009; Stritt and Knoll, 2010). In SRF-deficient mice primary hippocampal or dorsal root ganglia (DRG) neurons, neurite outgrowth is severely impaired (Knoll et al., 2006; Wickramasinghe et al., 2008). Conversely, overexpression of constitutively active SRF–VP16 enhanced neurite outgrowth in wild-type (Wickramasinghe et al., 2008) and was more pronounced in neurons with SRF-deficiency (Knoll et al., 2006). Thus, in general terms, SRF loss-of-function (LOF) decreases neurite growth. SRF gain-of-function (GOF), e.g., by overexpression of SRF–VP16, stimulates neurite extension (Table 1). The latter finding is of potential relevance in axonal regeneration (see SRF and Cofactors in Pathological Neuronal Motility and Potential SRF and Cofactor Invoked Mechanisms Modulating Neurite Growth and Regeneration).

Growth cones of SRF-deficient neurons do not protrude finger-like filopodia and therefore appear rounded in shape (Knoll et al., 2006; Stern et al., 2009) (Figure 1). Notably, retraction bulbs, the growth cone equivalent of transected CNS axons, are likewise rounded-up and frequently also protrude fewer filopodia (Erturk et al., 2007) (Figure 1). Stimulation of growth cone cytoskeletal dynamics with axon guidance cues, such as ephrins (Knoll and Drescher, 2002), results in a transient de-polymerization of the cytoskeleton, the so-called growth cone collapse response (Dent and Gertler, 2003; Pak et al., 2008). The growth cone collapse is thought to allow for directional re-orientation of axons ensuring appropriate axonal target selection in vivo. However, in Srf mutant neurons, actin, (and microtubule) cytoskeletal rearrangements upon guidance cue application failed. This resulted in aberrant growth cone structures consisting of F-actin and microtubule ring-like filaments (Knoll et al., 2006; Stern et al., 2009) (Figure 1). Similar results were also observed in endothelial cells lacking SRF, arguing for an SRF function on cytoskeletal dynamics conserved in various cell types (Franco and Li, 2009).

Serum response factor ablation in the adult nervous system revealed essential SRF functions in neuronal activity-induced gene expression, synaptic plasticity, learning, and memory (Ramanan et al., 2005; Etkin et al., 2006). Here, the IEG Arc, also possessing actin cytoskeleton modulatory properties (Messaudou et al., 2007), emerges as an important SRF and MRTF controlled target gene (Kawashima et al., 2009; Pintchovski et al., 2009; Smith-Hicks et al., 2010). Such an SRF-Arc regulatory unit might be instrumental in structural alterations of synapse function (e.g., spine growth and shape).

**MRFT Functions in Neuronal Motility**

**In vivo** function of MRTFs in the brain have recently been investigated employing Mrtf-a/Mrtf-b compound mouse mutants (Mokalled et al., 2010). Srf and Mrtf double mutants share many neuronal phenotypes, suggesting that SRF might mediate many of its functions by MRTF recruitment. Similar to neurons lacking SRF (see SRF Functions in Neuronal Motility), MRTF-A/MRTF-B deficient neurons revealed decreased neurite outgrowth (Mokalled et al., 2010). This is in line with overexpression of dominant-negative MRTF-A in primary hippocampal neurons resulting likewise in decreased neurite growth (Knoll et al., 2006; Shiota et al., 2006). In addition, MRTF-B overexpression or knock-down stimulates and reduces neurite complexity of primary neurons, respectively (Ishikawa et al., 2010; O’sullivan et al., 2010). In contrast MRTF-A knock-down resulted in enhanced neurite complexity, which might be explained by concomitant induction of MRTF-B expression (O’sullivan et al., 2010).

In summary, all data available so far point at a neurite outgrowth promoting function of MRTFs.
Table 1 | Summary of effects imposed on neuronal morphology upon SRF, MRTF and TCF loss-of-function (LOF) and gain-of-function (GOF).

|                  | SRF | MRTF | TCF |
|------------------|-----|------|-----|
| **Effect on**    | LOF | LOF  | LOF |
| Neuronal         |     |      |     |
| Morphology       |     |      |     |
| (i) Decreased    |     | (i)  | (i) |
| Neurite          |     | Enhanced | Enhanced |
| Outgrowth        |     | neurite | dendritic |
| (ii) Impaired     |     |     |     |
| Growth Cone      |     |     |     |
| Morphology       |     |     |     |
| (i) Decreased    |     |     |     |
| Neurite          |     |     |     |
| Outgrowth and    |     |     |     |
| Dendritic        |     |     |     |
| Complexity       |     |     |     |
| Reduced          |     |     |     |
| Dendritic        |     |     |     |
| Length           |     |     |     |
| (ii) Impaired     |     |     |     |
| Growth Cone      |     |     |     |
| Morphology       |     |     |     |
| (ii) Increased   |     |     |     |
| Neurite          |     |     |     |
| Branching        |     |     |     |
| (iii) Enhanced   |     |     |     |
| Neuronal         |     |     |     |
| Differentiation  |     |     |     |
| (iii) Enhanced   |     |     |     |
| Cell Death       |     |     |     |
| Method           |     | Overexpression |     |
| Conditional      |     | of SRF-VP16 | of const.-active |
| Murine Srf       |     |     | Elk-1 |
| Inactivation     |     |     |     |
| Overexpression   |     |     |     |
| of Mrtf-a/Mrtf-b |     |     |     |
| Inactivation     |     |     |     |
| (ii) siRNA       |     | Overexpression | Overexpression |
| Mediated Knock-  |     | of dom.-neg.  | of wt Elk-1 or |
| Down             |     | Elk-1     | sElk-1    |
| (iii) Overexpression |     |     |     |
| of dom.-neg. Mrtf-A |     |     |     |
| Cell Type        |     | Hippocampal, Cortical | Striatal |
| DRG              | Hippocampal, Cortical, DRG | Cortical | Striatal |
| Reference        |     | Hippocampal, Cortical, DRG | Cortical | Striatal |

**FIGURE 1 | Comparison of SRF-deficient growth cones with retraction bulb.** (A) Scheme of a growth cone of a wild-type neuron grown in cell culture. The growth cone typically protrudes multiple finger-like filopodia (one is marked by an arrow). (B) A growth cone derived from an SRF-deficient neuron grown in culture. Please note the reduced number of filopodia resulting in a round shape of the growth cone. (C) A so-called retraction bulb, typically found at the end of a transected axon of a wild-type neuron in vivo. Similar to SRF-deficiency, retraction bulbs elaborate fewer filopodia. Schematic drawing is based on a figure from Erturk et al. (2007).

**TCF FUNCTIONS IN NEURONAL MOTILITY**

Data available reveal a function of the TCF family member Elk-1 in neurite outgrowth and – of potential relevance for axonal regeneration – also in neuronal survival/apoptosis (Sgambato et al., 1998; Vanhoutte et al., 2001; Barrett et al., 2006a,b; Lavaur et al., 2007; Demir et al., 2009, 2011; Besnard et al., 2011; see Potential SRF and Cofactor Invoked Mechanisms Modulating Neurite Growth and Regeneration). An additional feature of TCFs shared by MRTFs, yet not SRF, is a potential nuclear-to-cytoplasmic shuttling of these gene regulators (Besnard et al., 2011). Wild-type Elk-1, in contrast to a shorter neuron-specific nucleus-restricted Elk-1 isoform (sElk-1), also localizes to the neuronal cytoplasm (Sgambato et al., 1998; Vanhoutte et al., 2001). Upon stimulation however, activated, i.e., phosphorylated Elk-1 appears to re-localize exclusively to the nucleus in vitro. However, in vivo neuronal activation resulted in both constitutive nuclear P-Elk-1 accumulation but also additional cytoplasmic signals (Lavaur et al., 2007). Thus, cytoplasmic vs. nuclear Elk-1 localization might also differentially influence neurite outgrowth. Indeed, nucleus-restricted sElk-1 enhanced the percentage of neuronal-like PC12 cell with neurites (Vanhoutte et al., 2001). Contrastingly, targeting Elk-1 overexpression specifically to the dendrites, resulted in decreased neuronal survival of primary neurons (Barrett et al., 2006a). Overexpression of dominant-negative or constitutively active Elk-1 resulted in Elk-1 localization primarily in the dendrites and nucleus of primary neurons, respectively. Whereas dominant-negative Elk-1 reduced dendritic length, the constitutively active Elk-1 enhanced dendritic length (Lavaur et al., 2007).

So far, TCF analysis in neurons in vivo failed to uncover essential TCF functions in the brain as detailed for SRF and MRTFs above. Investigations of TCF functions are hampered by an apparent functional redundancy among the three main family members.
Elk-1 mouse mutants reveal no obvious neuronal phenotype besides a mildly impaired IEG response in the hippocampus (Cesari et al., 2004).

In sum, Elk-1 modulates neuronal motility most likely in a sub-cellular compartment dependent manner.

**SRF AND COFACTORS IN PATHOLOGICAL NEURONAL MOTILITY**

As described in detail above (see SRF and Its Cofactors in Physiological Processes Requiring Neuronal Motility), SRF and cofactors were assigned various functions in shaping neuronal morphology including neurite growth, branching and growth cone shape. Many neurological disorders affect neuronal motility. Chronic seizures for instance, induce exuberant sprouting of mossy fibers emanating from dentate gyrus granule cell neurons. In contrast to this excessive outgrowth of new neurites during status epilepticus, axotomy in the central nervous system, e.g., during spinal cord injury, prevents re-growth of severed nerve fibers.

Due to its intimate link with actin cytoskeletal dynamics, activity of SRF and cofactors might be targeted during such neuro-pathological processes of neuronal motility. Particularly, the potential of SRF–VP16 to stimulate neurite outgrowth (Knoll et al., 2006; Wickramasinghe et al., 2008) and branching (Stritt and Knöll, 2010) of primary neurons might prove valuable for speeding up re-growth and branching of transected axons. In recent years, expression and/or functions of SRF and cofactors has been reported in the course of many neuro-pathological conditions. These include Alzheimer’s disease (Chow et al., 2007; Bell et al., 2009; Sharma et al., 2010), Huntington’s disease (Sharma et al., 2010), epilepsy (Herdegen et al., 1997a; Morris et al., 1999; Hu et al., 2004), de-myelination (Stritt et al., 2009), retinal degeneration (Sandstrom et al., 2011), hyperactivity (Parkina et al., 2010), hypoxia (Jiang et al., 2009; Cao et al., 2011), resilience to chronic stress (Vialou et al., 2010), and alcohol addiction (Paul et al., 2010). However so far, functional data of SRF or one of its cofactors in axonal regeneration are not available. Yet looking at regeneration processes in other organs, SRF has already been implicated in, e.g., ulcer healing, muscle, and hepatocyte regeneration (Chai and Tarnawski, 2002).

Interestingly, most data on roles of SRF and its cofactors in axonal injury available so far are derived from investigations focusing on TCFs, namely Elk-1. This might be due to the intimate link of TCFs such as Elk-1 and induction of an IEG response upon axonal injury (see Potential SRF and Cofactor Invoked Mechanisms Modulating Neurite Growth and Regeneration).

As indicated above, so far functional data on SRF and cofactors in axonal regeneration are not reported. However, expression profiles of SRF and TCFs, but not MRTFs, after axonal injury have been investigated (Herdegen and Zimmermann, 1995; Herdegen et al., 1997a; Lin et al., 2003; Hu et al., 2004; Sung et al., 2004; Perlson et al., 2005; Kerr et al., 2010).

In a first study, Perlson et al. (2005) demonstrated up-regulation of activated Elk-1 (P-Elk-1) in the nucleus within 10 min after DRG neuron axotomy. Notably, this P-Elk-1 induction was abolished in mice lacking the intermediate filament vimentin (Perlson et al., 2005). This increase in P-Elk-1 is most likely not due to novel Elk-1 mRNA synthesis, as recently demonstrated (Kerr et al., 2010). In this study, mRNA levels of various TCF family members were analyzed upon sciatic nerve lesion. Whereas Net (Elk-3) mRNA expression was strongly induced upon lesion, Elk-1 mRNA abundance remained unaltered. The induction of nucleus-restricted P-Elk-1 on protein level observed in lesioned DRG neurons (Perlson et al., 2005) was confirmed in a mouse model of traumatic brain injury in the hippocampal system (Hu et al., 2004). Further, elevated P-Elk-1 levels were observed in an *Aplysia* model of nerve crush (Lin et al., 2003; Sung et al., 2004). These findings suggest that Elk-1 activity in injured neurons is mainly regulated by post-translational, i.e., phosphorylation, rather than transcriptional mechanisms.

A first study analyzing both Elk-1 and SRF in neuronal injury was provided by Lin et al. (2003). Here, the authors provide data arguing for occupancy of a *c-fos* derived SRE by Elk-1 and SRF in both injured pleuropedal *Aplysia* and mouse DRG neurons. In contrast to DRG neurons, altered SRF expression was not found in other peripheral neuron lesion models including the optic and facial nerve (Herdegen et al., 1997a).

In sum, although far from being complete, data available so far mainly focusing on peripheral nerve injury indicate that Elk-1 and also SRF activity are targeted by axonal transection. Future studies will have to address SRF and cofactor expression also in central axon injury models. In addition, it will be important to expand analysis to various (short and longer) time-points after injury also including additional SRF and cofactor anti-sera.

**POTENTIAL SRF AND COFACTOR INVOKED MECHANISMS MODULATING NEURITE GROWTH AND REGENERATION**

Serum response factor and cofactors can potentially regulate a wealth of different target genes, depending on, e.g., cell and stimulus type. As outlined above (see Introduction), SRF-mediated gene regulation has been analyzed in greatest depth in the IEG response and for genes encoding components of the actin cytoskeleton. Therefore, I will propose potential mechanism by which SRF and cofactors might modulate neuronal motility involving IEGs and cytoskeletal gene products.

**IEG ACTIVATION AND NEURONAL FUNCTIONS**

The induction of IEGs, primarily those encoding transcriptional regulators such as c-Jun, by axonal injury is a well-established response observed in various neuronal populations (Morgan et al., 1987; Haas et al., 1993; Hull and Bahr, 1994; Carran and Morgan, 1995; Robinson, 1995; Herdegen et al., 1997a,b; Herdegen and Leah, 1998; Herdegen and Waetzig, 2001; Moran and Graeber, 2004; Raivich et al., 2004; Raivich and Behrens, 2006; Raivich, 2008). Besides changes in expression level, individual IEGs such as c-Jun are indispensable for peripheral axon regeneration, e.g., of facial motor neurons (Raivich et al., 2004). IEG induction is rapid, yet transient, suggesting an involvement of IEGs in early stages of neuronal differentiation and axonal injury processes. Of note, many IEGs encode transcription factors (*c-Fos*, *Egr-1*, *Egr-2*, *Fosb*, *JunB*, *c-Jun*) under SRF-mediated gene transcription (Posern and Treisman, 2006; Knöll and Nordheim, 2009; Olson and Nordheim, 2010). Thus, a hierarchical cascade of gene regulators with SRF acting upstream of IEGs might operate and
Serum response factor (Chang et al., 2004) and MRTF (Cao et al., 2011) overexpression protects neurons from cell death in cell culture. In contrast, in vivo no major SRF contribution to regulation of neuronal cell survival and apoptosis during brain development and physiological function has been reported (Knoll and Nordheim, 2009).

Besides apoptosis/cell survival, IEGs such as Egr-1, c-Fos and c-Jun may directly modulate neurite outgrowth in vitro (Jessen et al., 2001; Levkovitz et al., 2001; Eminel et al., 2008). However, enhanced neurite outgrowth might be coupled with or as a consequence of a potential pro-survival IEG function. In addition, the IEG Arc – also controlling actin cytoskeletal dynamics – is regulated by synaptic activity (Plath et al., 2006; Smith-Hicks et al., 2010) summarized in (Shepherd and Bear, 2011). Thus, SRF-controlled IEGs might not only contribute to early phases of axonal regeneration when survival/cell death decisions are made, but also at later stages, e.g., during synaptic targeting and function of successfully regenerated axons.

**CYTOSKELETAL DYNAMICS AND NEURONAL MOTILITY**

Along with microtubules, actin is a major cytoskeletal component involved during neuronal motility (Dent and Gertler, 2003; Pak et al., 2008; Tahirovic and Bradke, 2009). In contrast to microtubules (Erturk et al., 2007) which have been extensively investigated in retraction bulbs of injured axons in vivo, the actin cytoskeleton has not been analyzed so far in the same depth. Also, whereas interference with microtubule function enhances axonal regeneration in vivo (Hellal et al., 2011), depletion of the major neuronal actin variant β-actin did not affect motor axon regeneration in vivo (Cheever et al., 2011). In line with this, overexpression of β-actin in SRF-deficient neurons alone was not sufficient to rescue neurite outgrowth (Knoll et al., 2006). This might suggest that ABPs and/or other actin isoforms (e.g., α-actin or γ-actin) are more crucial for neurite outgrowth and axonal regeneration processes. Indeed, actin isoforms (Tetzlaff et al., 1988, 1991; Mizobuchi et al., 1990; Tetzlaff and Bisby, 1990; Bisby and Tetzlaff, 1992; Lund and Mcquarrie, 1996; Riley and Bernstein, 1996; Lund et al., 2002; Awwenagha et al., 2003; Moran and Graeber, 2004; Willis et al., 2005) and ABPs such as thymosin (Mollinari et al., 2009), myosins (Jian et al., 1996), GAP-43 (Tetzlaff et al., 1991; Lund and Mcquarrie, 1996; Riley and Bernstein, 1996; Lund et al., 2002; Awwenagha et al., 2003), integrins (Werner et al., 2000), and, e.g., coronins (Di Giovanni et al., 2005) are up-regulated upon axonal injury in various instances. Myosin expression has been shown to overcome in vitro neurite outgrowth barriers associated with axonal regeneration (Kubo et al., 2008). As genes encoding myosin components are SRF-regulated (Knoll and Nordheim, 2009; Olson and Nordheim, 2010), SRF might contribute to neurite outgrowth processes in development and pathology by transcriptional regulation of myosin and other promoters regulating expression of actin associated genes (Figure 2).

Besides transcriptional regulation, SRF can modulate activity of the actin severing proteins cofilin and gelsolin (Alberti et al., 2005; Mokalled et al., 2010). Elevated P-cofilin levels, representing inactive cofilin, were reported in SRF- and MRTF-deficient neurons (Alberti et al., 2005; Mokalled et al., 2010). This suggests that wild-type SRF–MRTF signaling activates cofilin, a mechanism involving the CDK5 interacting kinase Pctaire1 (Mokalled et al.,...
Inactive cofilin might prevent actin treadmilling and, e.g., SRF-mediated transcription (Chang et al., 2004; Kalita et al., 2006), suggesting important for conveying SRF’s impact on neuronal motility. In turn, SRF-deficiency altered Rho-GTPase activity (Stritt and Knoll, 2010), suggesting a tight regulatory loop between Rho-GTPases and SRF. Rho-GTPases, particularly RhoA are well-known downstream effectors mediating the growth inhibitory potential of Nogo, MAG and other myelin associated regeneration inhibitors (Filbin, 2003; Yiu and He, 2006). In addition, Rho-GTPases modulate neuronal motility, e.g., neurite outgrowth and polarization (Govek et al., 2005; Tahirovic and Bradke, 2009; Hall and Lalli, 2010). Thus, although data are currently not available, it might be tempting to speculate that Rho-GTPases interact with SRF-mediated transcription during physiological and regenerative neuronal motility processes (Figure 2). As so far, MRTFs have been shown to connect Rho-GTPase–actin with SRF signaling, it is likely that MRTFs are the crucial cofactors teaming up with SRF during these functions.

SRF’s IMPACT ON GROWTH FACTOR SIGNALING IN NEURONAL MOTILITY

Many growth factors modulate neurite outgrowth and axonal regeneration. With regard to neuronal SRF-mediated transcriptional regulation, two growth factor signaling pathways might prove important for conveying SRF’s impact on neuronal motility. First, neurotrophins such as BDNF and NGF activate SRF-mediated transcription (Chang et al., 2004; Kalita et al., 2006; Wickramaingeshe et al., 2008; Stritt and Knoll, 2010) and SRF expression (Kalita et al., 2006). Data available so far suggest a recruitment of MAP kinases upon neurotrophin signaling to activate SRF. As neurotrophins are implicated in neuronal survival, neurite outgrowth, growth cone morphology, and axonal regeneration (Galbo and Letourneau, 2004; Lykissas et al., 2007), SRF, and cofactors might be targeted by signaling cascades triggered by neurotrophins. Additionally, Bdnf mRNA levels were reduced in Srf mutant neurons, suggesting induction of the Bdnf promoter by wild-type SRF (Etkin et al., 2006). Thus, SRF might be employed to adjust BDNF levels available to neurons and thereby influence axonal injury (Figure 2).

Secondly, SRF emerges as transcriptional regulator of many genes encoding components of insulin or insulin growth factor (IGF) signaling in neurons and non-neuronal cells. These genes include the insulin gene (Sarkar et al., 2011), Igf1 (Charvet et al., 2006; Sun et al., 2009), and, e.g., Ctgf, a protein harboring an IGF binding domain (Stritt et al., 2009). Such SRF-mediated control of insulin/IGF regulation in neurons was also demonstrated to affect neighboring cells, i.e., oligodendrocytes, in a paracrine manner (Stritt et al., 2009). In addition, insulin signaling augmented TCF occupancy at SREs (Thompson et al., 1994) and insulin resistance in muscles is associated with altered SRF–MRTF activity (Jin et al., 2011). Notably, insulin/IGF signaling regulates neurite outgrowth (Ozdinler and Macklis, 2006) and can increase regeneration properties of transected axons (Near et al., 1992; Ishii et al., 1994; Fu and Gordon, 1997). SRF might also be connected to glial scar formation, a major physical barrier of CNS axon regeneration. This might be accomplished by regulation of Ctgf (connective tissue growth factor) levels, a secreted protein associated with fibroactin function and scar formation (Hertel et al., 2008; Conrad et al., 2005).

In sum, SRF gene regulation might modulate insulin/IGF signaling during physiological neuronal motility processes as well as in injured neurons (Figure 2).

OUTLOOK

Wild-type SRF and cofactors can modulate many mechanisms such as an IEG response, actin cytoskeletal dynamics, and growth factor signaling which contribute to neuronal motility in development and, e.g., axonal injury. Future experiments will have to address directly, e.g., employing conditional Srf or Mrtf mutagenesis or TCF compound mutants, whether SRF and cofactors are key players in axonal regeneration. In this regard, performing GOF experiments employing SRF–VP16, a known in vitro stimulator of neurite outgrowth, in in vivo axonal regeneration paradigms might be particularly rewarding.

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