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Multiple Transcription Factor Families Regulate Axon Growth and Regeneration

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Abstract

Understanding axon regenerative failure remains a major goal in neuroscience, and reversing this failure remains a major goal for clinical neurology. While an inhibitory CNS environment clearly plays a role, focus on molecular pathways within neurons has begun to yield fruitful insights. Initial steps forward investigated the receptors and signaling pathways immediately downstream of environmental cues, but recent work has also shed light on transcriptional control mechanisms that regulate intrinsic axon growth ability, presumably through whole cassettes of gene target regulation. Here we will discuss transcription factors that regulate neurite growth in vitro and in vivo, including p53, SnoN, E47, CREB, STAT3, NFAT, c-Jun, ATF3, Sox11, NFκB, and Kruppel-like factors (KLFs). Revealing the similarities and differences among the functions of these transcription factors may further our understanding of the mechanisms of transcriptional regulation in axon growth and regeneration.

INTRODUCTION

Recent years have seen remarkable advances in our molecular understanding of the failure of axon regeneration in the central nervous system (CNS). Soon after becoming post-mitotic, neurons extend their axons to connect to their targets. When axons are damaged either after injury or in degenerative diseases, their failure to reconnect, or regenerate back to these original targets leads to permanent dysfunction and, ultimately, disability. The capacity of neurons to regenerate their axons largely depends on the location of the axons in the nervous system, and their stage of development. Axons in the peripheral nervous system (PNS) can regrow to their peripheral targets, whereas axons in the central nervous system (CNS) cannot. Glial-associated inhibitors of regeneration and their neuronal receptors and downstream signaling pathways clearly contribute to CNS regenerative failure, but there is also a role for cell-autonomous regulation of axon growth ability, which may depend on environmental cues or be regulated intrinsically.

Transcription factors are uniquely positioned for cell-autonomous regulation of axon growth ability, as they may regulate sets of gene targets that enhance or suppress regeneration. Indeed, using methods to globally assay gene expression such as microarrays, a number of groups have demonstrated genes expression regulation during development and after axon injury, in different model systems and cell types, and in neurons that may or may not regenerate. Furthermore, distinct changes in gene expression are observed at different timepoints after injury. Immediately after injury, there are increases in the expression of transcription factors, while structural and neurotransmission genes are downregulated (for review, see (Bareyre and Schwab, 2003). This early activation of a transcriptional program

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is clearly important, as many subsequent target genes have been demonstrated to be critical for successful regeneration. Blocking transcription at an early time point after injury changes regenerative response (Smith and Skene, 1997). At later time points, there is an increase in expression of stress-associated genes concurrent with a decrease in cytoskeletal and synaptic genes (for review, see (Bareyre and Schwab, 2003). In neurons that regenerate, there is a large increase in the expression of regeneration-associated genes after injury (Bosse et al., 2001; Schmitt et al., 2003; Bosse et al., 2006). Furthermore, in peripheral sensory neurons, injury of peripheral branches that regenerate leads to greater changes in gene expression than injury of central branch of the same neurons, which do not regenerate (Hoffman, 2010).

What causes these changes in gene expression after axon injury? Transcription factors are DNA-binding proteins able to activate or repress expression of their target genes. Their effects are amplified by their ability to bind to multiple locations on the genome resulting in a large number of genes being turned on or off by a single transcription factor. After injury, the upor downregulation of transcription factors, and post-translational modification of transcription factors already expressed in the cell, begin a cascade of signaling events leading to specific gene expression changes.

While it is clear that transcriptional changes are important in axon growth and regeneration, they are most often studied at the level of the genes that are modulated and not of the transcription factors that regulate them. Studies mapping the promoter regions of genes identified in microarray experiments can identify common binding sites for transcription factors, leading to identification of gene expression programs elicited by specific transcription factors in particular situations. This can also be studied by chromatin immunoprecipitation (ChIP) experiments, allowing for identification of physiological binding sites for that transcription factor in that specific circumstance. While most studies focus on the specific downstream gene that could be involved in increasing regeneration, it is highly likely that the combination of genes that are activated/repressed by a collection of transcription factors lead to the specific regenerative abilities of neurons during development or after injury.

Thus, transcription factors are powerful proteins, capable of orchestrating complex axon growth and regenerative responses. Here we review transcription factors that have been studied for their role in axon growth and regeneration. Many interesting complexities of gene regulation are shared by these transcription factors, from competition to redundancy, activation to repression, and co-factor recruitment to post-translational modification. We will discuss some of these complexities as they relate to deciphering how transcriptional control of axon growth may be modulated to enhance regeneration in the CNS.

p53

p53 is a member of a family of tumor suppressors together with p63 and p73. Its cellular functions range from inducing apoptosis, to inhibiting cell cycle progression, to increasing DNA repair. Associated with these functions, p53 is estimated to be mutated in over half of all cancers (Vogelstein et al., 2000; Bargonetti and Manfredi, 2002). In the nervous system, p53 has been studied primarily for its pro-apoptotic role, for example, after neurotrophin withdrawal in sympathetic neurons, following injury, and in neurodegenerative diseases (Miller et al., 2000; Morrison et al., 2003; Culmsee and Mattson, 2005). p53 family members are also able to antagonize cell death (Jacobs et al., 2006). How and why p53 displays this bifunctional role in survival remain important, unanswered questions.

Role of p53 in Neurite Growth and Regeneration

The close relationship between survival and axon regeneration in neurons has been difficult to separate (Goldberg and Barres, 2000). In the CNS, p53 is developmentally regulated and expressed more in the developing than the adult brain (Gottlieb et al., 1997; Komarova et al., 1997). In vitro and in vivo, p53 promotes neurite growth. Overexpression of a dominant negative form of p53 in primary cortical neurons leads to a decrease in neurite outgrowth. This decrease in neurite growth is associated with a coincident decrease in the expression of three p53 target genes whose protein products are growth cone-associated and also promote neurite growth: Coronin1b, Rab13, and GAP-43 (Di Giovanni et al., 2005; Di Giovanni et al., 2006). Other genes involved in axon guidance such as netrins and their receptors, semaphorins and their receptors, ephrins and their receptors, and slits are also regulated by p53 (Arakawa, 2005). In vivo in a peripheral facial nerve injury model, p53 knockout (KO) mice demonstrated a significant decrease in the number of regenerating fibers when compared with wildtype (WT) control animals, suggesting an in vivo role for p53 in axon regeneration in the PNS (Di Giovanni et al., 2006). Associated with these effects, overexpression of WT p53 leads to an increase in growth cone size, whereas overexpression of a dominant negative form or a version of p53 lacking an export signal, causes growth cone collapse, though this may be due to non-transcriptional mechanisms (Qin et al., 2009). If p53 is important for neurite growth, then its absence in the adult CNS correlates with the reduced regenerative ability of adult CNS neurons.

Effects of Post-Translational Modifications on Function

Post-translational modifications regulate p53's ability to increase neurite growth (Tedeschi and Di Giovanni, 2009). p53 can undergo multiple types of post-translational modifications including acetylation, phosphorylation and ubiquitination (Lavin and Gueven, 2006), which can affect localization and function. For example, in a non-transcriptional setting, phosphorylated p53 associates with Tau but not MAP2 and is primarily localized to axons and growth cones, whereas acetylated p53 is present in axons, but not in growth cones (Qin et al., 2009). Looking at target gene regulation, overexpression of p53 mutated to include an acetylation mimic at lysine 320 (K320Q) but not at lysine 372 increases expression of downstream targets. The $p53^{K320Q}$ acetylation mimic in cortical neurons increases neurite length, whereas a non-acetylatable p53 mutant decreases neurite growth. The acetylation of p53 at specific lysines by the acetyltransferase CBP/p300 results in an increased ability of the transcriptional unit CBP/p300/Ac-p53 to occupy the GAP-43 promoter and increase GAP-43 expression. p53 is acetylated at multiple sites (K372, K373, and K382) by CBP/p300 and together they are recruited to bind to the GAP-43 promoter (Tedeschi et al., 2009). Interestingly, acetylation at p53's C terminus does not lead to cell death in cortical neurons (Tedeschi and Di Giovanni, 2009), but leads to apoptosis in cell lines (Gu et al., 2004; Knights et al., 2006; Tang et al., 2008; Yamaguchi et al., 2009). Thus, the function of this transcription factor depends largely not only on its post-translational modifications, but also the cell-specific intracellular environment.

Taken together, these studies suggest a role for p53 in modulating neurite growth and regeneration. These effects may be largely mediated through p53's downstream targets; however, a local function for p53 at the growth cone may also contribute. Given p53's well-described role in apoptosis in neurons and non-neuronal cells, it will be important to continue to monitor for effects on neuronal survival even while studying neurite growth and axon regeneration.

c-JUN

The activator protein-1 (AP-1) transcription factor complex is made up of homo- and heterodimers from the Jun family of proteins (c-Jun, JunB, JunD), Fos proteins (c-Fos, FosB, Fra-1, Fra-2), the ATF family, and other bZIP-containing transcription factors (Jochum et al., 2001), as well as MyoD, NFAT, and CBP (Herdegen and Leah, 1998). As there are many AP-1 binding sites throughout the genome, dimerization variety likely contributes to specificity in transcriptional target regulation.

c-Jun Expression in the Nervous System

c-Jun expression is induced after injury or stress (Herdegen and Waetzig, 2001; Raivich, 2008). Developmentally, it is highly expressed during embryogenesis (Wilkinson et al., 1989; Bennett et al., 1997) and through postnatal day 15 (P15) in the CNS (Mellstrom et al., 1991), after which expression decreases to a lower basal level throughout adulthood (Herdegen et al., 1991; Raivich and Behrens, 2006).

c-Jun Response After Injury

What is c-Jun's function after injury? In many neurons, inhibition of c-Jun after axotomy delays cell death (Crocker et al., 2001; Lingor et al., 2005). Conversely, an unphosphorylatable c-JunAA mutant expressed in CA3 pyramidal hippocampal neurons protects against kainic acid-induced cell death, suggesting phosphorylated c-Jun contributes to apoptosis after injury (Behrens et al., 1999). Despite these data, in other models c-Jun upregulation is associated with surviving neurons (Herdegen et al., 1993). For example, after optic nerve injury and subsequent peripheral nerve graft, surviving RGCs express c-Jun for up to a month (Hull and Bahr, 1994; Robinson, 1994; Robinson, 1995).

c-Jun may also be involved in the axonal regenerative response after injury in the nervous system. Regenerating neurons upregulate c-Jun (Herdegen et al., 1991; Jenkins and Hunt, 1991; Leah et al., 1991; Herdegen et al., 1997; Lindwall and Kanje, 2005). For example, peripheral neurons upregulate c-Jun after peripheral, sciatic nerve lesion, but not after a central lesion of these same neurons' axons, correlating with regenerative response (Broude et al., 1997). Manipulations to increase central regeneration such as transplanting embryonic spinal cord tissue (Broude et al., 1997) or grafting peripheral nerves into injury sites (Hull and Bahr, 1994; Robinson, 1994; Robinson, 1995; Vaudano et al., 1998) are similarly associated with an increase in c-Jun expression, but typically only in successfully regenerating neurons.

How does axon injury lead to c-Jun expression and/or activation? Treatment with antibodies against the neurite growth inhibitor Nogo increase c-Jun expression in Purkinje cells, as does application of colchicine to block axonal transport, suggesting an inhibitory signal may be retrogradely transported from the axon to stop c-Jun expression and regeneration-associated genes (Zagrebelsky et al., 1998). On the other hand, c-Jun N-terminal kinase (JNK) is retrogradely transported in injured axons to activate c-Jun in the nucleus after peripheral nerve injury, as blockade of retrograde transport inhibits c-Jun activation (Lindwall and Kanje, 2005). These opposing results could be due to differences between the PNS and CNS, and further studies may address the function of retrograde transport on c-Jun expression and activation after injury.

Role of c-Jun in Neurite Growth and Regeneration

c-Jun expression correlates with axon regeneration, but does it play a functional role? Conditional c-Jun knockout mice as well as transgenic mice overexpressing c-Jun have been studied to address c-Jun's role in survival and regeneration. In nestin-promoted c-Jun

knockout mice, there was a decrease in regeneration and sprouting following facial nerve axotomy and in expression of regeneration-associated target genes such as CD44, galanin and α7β1 integrin (Raivich et al., 2004). In contrast, c-Jun overexpressing transgenic mice did not demonstrate increased Purkinje cell regeneration into a growth-permissive graft (Carulli et al., 2002). Taken together, these transgenic models suggest that c-Jun may be necessary but not sufficient to increase regeneration in CNS neurons.

Effects of Post-Translational Modifications on Function

c-Jun activity can be up- or downregulated by post-translational modifications. For example, mutating the Ser-73 phosphorylation site leads to a reduced number of PC12 cells with neurites, whereas mutation of the Ser-63 phosphorylation site leads to an increased number of cells with neurites (Dragunow et al., 2000). One of the upstream kinases responsible for phosphorylating c-Jun is the c-Jun N-terminal kinase (JNK), a member of the stress-activated protein kinases (SAPKs) and mitogen-activated protein kinases (MAPKs). JNKs have many targets, but they can, at a minimum, activate c-Jun by phosphorylation on both serines 63 and 73 (reviewed by (Waetzig et al., 2006). Neuronal injury increases JNK-mediated c-Jun phosphorylation (Herdegen et al., 1998), and application of a JNK inhibitor to explants of injured DRGs or nodose ganglia (NG) reduces c-Jun phosphorylation, ATF3 expression, and neurite outgrowth, without affecting survival (Lindwall et al., 2004). This demonstrates that after peripheral nerve injury, activation of JNK leads to phosphorylation of c-Jun and an increase in neurite outgrowth.

Thus, the majority of reports suggest that c-Jun is upregulated in regenerating neurons after injury, and that it can function to increase neurite growth. In addition, c-Jun expression decreases during development in a manner reflective of the loss of axon growth and regenerative ability in the mammalian CNS.

ATF3

Activating transcription factor 3 (ATF3) is a member of the ATF/CREB (cAMP-responsive element binding protein) family of basic leucine zipper domain (bZIP) transcription factors. All members of this group possess bZIP DNA binding domains, however, the homology of the rest of the protein separates the factors into specific subgroups (Hai et al., 1999). Interestingly, the consensus binding site for ATF factors is identical to the CRE consensus binding site (Hai and Hartman, 2001). Other names for ATF3 (in human) include LRF-1 (in rat), and LRG-21, CRG-5, and TI-241 (in mouse). ATF/CREB proteins can form heterodimers either with each other or with other bZIP proteins like members of the AP-1 family (such as Fos and Jun) and CCAAT-enhancer-binding proteins (C/EBPs), including ATF2, JunB, JunD, c-Jun, and gadd153/CHOP10 (reviewed by (Hai et al., 1999; Hai and Hartman, 2001). Heterodimer formation can selectively affect transcriptional regulation, leading to either activation or repression at specific promoters. ATF3 homodimer interactions generally result in transcriptional repression, and ATF3 can repress its own promoter creating a negative feedback loop (Wolfgang et al., 2000). Interestingly, ATF3 can activate promoters with no functional binding sites for ATF3, suggesting a function in sequestering co-repressors away from such promoters, and a naturally occurring ATF3 isoform lacking its DNA-binding domain (ATF3 delta Zip) activating transcription (Chen et al., 1994).

ATF3 Expression in the Nervous System

ATF3 expression levels are low in most cell types but increase with injury or stress. In the nervous system, for example, ATF3 is induced following seizures in the brain (Chen et al., 1996; Francis et al., 2004), peripheral nerve injury (Tsujino et al., 2000; Isacsson et al.,

2005; Seijffers et al., 2006), optic nerve injury (Takeda et al., 2000), and NGF depletion (Mayumi-Matsuda et al., 1999). Several pathways have been implicated in activating ATF3 expression following stress, such as JNK/SAPK and p53-dependent mechanisms. In addition, extracellular signals such as serum, FGF, EGF, HGF, PMA, cytokines and forskolin can also lead to ATF3 activation (reviewed in (Hai et al., 1999).

Role of ATF3 in Neurite Growth and Regeneration

Is ATF3 involved in neurite growth and regeneration? Similar to c-Jun, ATF3 is upregulated in regenerating neurons, for example after peripheral nerve transplantation to thalamic neurons (Campbell et al., 2005) or after intracortical but not spinal axotomy of layer V corticospinal neurons, in correlation with axon sprouting and growth (Mason et al., 2003). Similarly, injury to the central axons of DRG neurons results in very minimal increases in ATF3 expression (Seijffers et al., 2006). These studies suggest that ATF3 is upregulated in neurons that are successfully regenerating.

Can ATF3 overexpression increase regeneration? Transgenic overexpression in DRG neurons results in an increase in neurite outgrowth in vitro and increased peripheral nerve regeneration in vivo, similar in effect to a pre-conditioning lesion (Seijffers et al., 2007). Unlike pre-conditioning lesioned neurons, however, ATF3 overexpression did not increase DRG neurons' ability to grow on an inhibitory substrate, suggesting the mechanisms responsible for regenerating an axon are separate from those involved in overcoming glial-associated inhibition. Interestingly, injury to the central axons of DRG neurons resulted in no increase in regeneration in these same animals (Seijffers et al., 2007).

Mechanisms of Transcriptional Control

ATF3's repressed targets in non-neuronal cells include fibronectin, decorin, thrombospondin 2, and the pro-apoptotic Par-4 in transformed primary cultures of chick embryo fibroblasts (Perez et al., 2001), as well as p53 in human umbilical vein endothelial cells (HUVECs) (Kawauchi et al., 2002). In neurons, comparison of uninjured DRGs of WT and ATF3-transgenic mice, to sciatic nerve injured WT DRGs revealed increases in the expression of hsp27, Sprr1a, and c-Jun in ATF3-transgenic DRGs, though this was still considerably less than that seen with sciatic nerve-injured DRGs. Interestingly, other genes typically upregulated after peripheral nerve injury, such as GAP-43, CAP-23 and STAT3, were not increased in the ATF3-transgenic mice (Seijffers et al., 2007). This suggests that ATF3 overexpression alone in uninjured DRGs leads to a slight upregulation of some but not all growth-associated gene targets, and that ATF3 upregulation on its own is not enough to fully recapitulate the peripheral nerve regeneration program (Seijffers et al., 2007).

c-Jun and ATF3: A Special Combination

Are ATF3 and c-Jun expression coordinately regulated after injury and during neurite growth? ATF3 and c-Jun can form heterodimers, leading to transcriptional activation (Hai and Curran, 1991; Hsu et al., 1991; Hsu et al., 1992; Chu et al., 1994). Additionally, they are both induced following injury (Tsujino et al., 2000; Isacsson et al., 2005; Raivich and Behrens, 2006). Whereas ATF3 expression is virtually undetectable in naïve DRG and spinal cord, it is induced in both DRG and spinal cord motorneurons in vivo after peripheral injury, and phosphorylated c-Jun co-localizes with these ATF3-positive neurons (Tsujino et al., 2000; Lindwall et al., 2004). This suggests the possibility of heterodimerization, supported by co-immunoprecipitation in PC12 cells (Pearson et al., 2003). In addition, inhibiting JNK in this model leads to decreased activation of c-Jun and ATF3 expression as well as to decreased axon growth (Lindwall et al., 2004), though the specific mechanism behind this decreased axon growth is not clear.

Taken together, these studies suggest that ATF3 and c-Jun can act together to regulate transcription through heterodimerization. While their specific relationship in axon regeneration is still unclear, these studies suggest that their coincident upregulation may act synergistically to increase axon growth.

CREB

CREB (cAMP response element binding protein), a member of the ATF/CREB family of bZIP transcription factors (Hai and Hartman, 2001), is a transcriptional mediator of cAMP signaling in the nervous system (Hannila and Filbin, 2008). Together with CREM (cAMP response element modulator), ATFs and various CREB and CREM isoforms generated by alternate promoter usage and alternative exon splicing (Walker et al., 1996; Walker and Habener, 1996), CREB binds cAMP response elements (CREs) in DNA (Lonze and Ginty, 2002). As with all bZIP transcription factors, there is a requirement for homo- or heterodimerization through their zipper domain. CREB is necessary for activity-dependent transcriptional changes in learning and memory processes (for review (Kandel, 2001), and also plays important roles in addiction, circadian rhythms, and neuroprotection (for review (Lonze and Ginty, 2002).

Role of CREB in Neurite Growth and Regeneration

What is the effect of CREB on axon outgrowth and regeneration? CREB null mice display peripheral axon outgrowth deficits in vivo, and in vitro cultured DRG and SCG neurons from these mutants elaborate shorter neurites than controls. This suggests an importance of CREB for axon growth in PNS neurons (Lonze et al., 2002). In the CNS of CREB null mice, there were abnormalities in the development of the corpus callosum and anterior commissure (Rudolph et al., 1998). The importance of CREB for neurite growth in cultured neurons has been demonstrated in other studies using overexpression of a dominant negative CREB, which resulted in decreased dendritic outgrowth in cortical neurons and loss of the ability of cAMP or neurotrophins to increase neurite growth on an inhibitory substrate (Redmond et al., 2002). Conversely, injection of virus carrying a constitutively active CREB construct into the DRG prior to a dorsal column lesion increased axon regeneration through the lesion site at least 3 times greater than controls (Gao et al., 2004). Thus, CREB function plays an important role in neurite outgrowth in both the PNS and CNS.

Mechanisms of Transcriptional Control

What are the downstream targets of CREB signaling? One important target may be the enzyme arginase I (Arg I), important in the synthesis of polyamines which promote axon regeneration, for example of RGCs in vivo (Deng et al., 2009). Overexpression of a dominant negative CREB blocks the cAMP-mediated increase in Arg I expression, whereas overexpression of a constitutively active form of CREB significantly increases Arg I expression. It has not been determined if CREB activates Arg I expression through direct or indirect means, however, as Arg I has only a CRE half-site in its promoter (Gao et al., 2004). These studies suggest that activated CREB can regulate the expression of Arg I.

Other targets downstream of CREB include BDNF (Shieh et al., 1998; Tao et al., 1998; Finkbeiner, 2000; Mayr and Montminy, 2001) and many others identified by serial analysis of chromatin occupancy (SACO) in PC12 cells (Impey et al., 2004). It will also be important to study specific neuronal types, as gene targets of activated CREB may differ depending upon the cellular milieu, as, for example, CREB-regulated tyrosine hydroxylase (TH) is induced in sympathetic neurons, but not in hippocampal neurons (reviewed in (Lonze and Ginty, 2002). CREB's recruitment to DNA and effects on gene expression after neurotrophin treatment or activity may also be influenced by nitric oxide (NO) nitrosylation of HDAC2,

releasing it from DNA, thus leading to net acetylation and opening up new CREB targets (Riccio et al., 2006; Nott et al., 2008). This suggests that the gene regulation we see from transcription factors is highly reliant on the chromatin state and what promoters are available for binding. Interestingly, the CRE site contains a CpG dinucleotide which can be methylated, resulting in an inability of CREB to bind and activate transcription in vitro (Iguchi-Ariga and Schaffner, 1989). Thus chromatin state and the intracellular environment of each specific neuron may play a role in CREB's ability to regulate downstream targets.

CREB's Subcellular Localization

Recently, exciting work has suggested that axonal translation of CREB mRNAs may be involved in the nuclear phospho-CREB response leading to an increase in survival (Cox et al., 2008). Application of NGF to DRG axons in compartmentalized cultures activated TrkA receptors which induced local translation of CREB mRNA. Axonally derived CREB protein was then actively retrogradely transported along the axon to the cell body, possibly through association with the NGF-pTrkA signaling endosome. CREB became phosphorylated and once to the nucleus activated transcription of pro-survival genes (Cox et al., 2008). CREB mRNA is also present in dendrites of hippocampal neurons and can be locally translated, possibly phosphorylated, and transported to the nucleus (Crino et al., 1998). Interestingly, these authors did not see this effect in the axons, suggesting that there could be different regulation in different types of neurons and neurites. In any case, both of these studies suggest that transcription factors can be synthesized outside of the nucleus, and still contribute to nuclear gene expression regulation.

Effects of Post-Translational Modifications on Function

There are multiple phosphorylation sites on CREB that regulate CREB's ability to bind co-factors (Kornhauser et al., 2002). Phosphorylation of CREB at Ser-133 has been most studied. Neurotrophin treatment leads to CREB phosphorylation on Ser-133 (Riccio et al., 1997; Watson et al., 1999; Watson et al., 2001; Lonze et al., 2002; Arthur et al., 2004; Riccio et al., 2006; Spencer et al., 2008), which is then necessary for recruitment of the co-activator CBP (Chrivia et al., 1993; Kwok et al., 1994). CREB can be phosphorylated and activated by many kinases, including PKA, PKC, CAMKII, CAMKIV, AKT, MAPKAP K2, and members of both the RSK and MSK families (for review (Mayr and Montminy, 2001), and it is negatively regulated by phosphatases such as PP1 and PP2A, and possibly by phosphorylation of different residues (Sun et al., 1994). Calcium influx leads to phosphorylation of CREB at Ser-133, Ser-142 and Ser-143, important in CREB-dependent transcription (Sun et al., 1994; Kornhauser et al., 2002). CREB co-activators p300 and CBP act as adaptors for recruitment of RNA transcription machinery, and can also function to acetylate histones and non-histone proteins, opening DNA for transcription (Shaywitz and Greenberg, 1999). The co-activator CBP binds to CREB after its phosphorylation on Ser-133, and the ability of this complex to drive transcription relies heavily on binding strength (Shaywitz et al., 2000). These studies suggest an importance for specific phosphorylation in CREB activation or function. There is still little known, however, about how post-translational CREB modification regulates neurite growth and regeneration.

STAT3

Signal transducer and activator of transcription 3 (STAT3) is one of 7 mammalian STATs. STATs are typically found as unphosphorylated monomers or occasionally in high molecular weight complexes (Lackmann et al., 1998; Ndubuisi et al., 1999; Chatterjee-Kishore et al., 2000; Sehgal, 2008), waiting in the cytoplasm until they are activated by extracellular signals such as growth factors and cytokines. Ligand binding to cell-surface receptors leads to activation of the associated receptor tyrosine kinase Janus kinases (JAKs),

which phosphorylate tyrosine residues on receptor tails that act as binding sites for STAT proteins. STATs dock onto the phospho-tyrosines via their SH2 domain, and are also phosphorylated by JAK on a tyrosine residue. Immediately following phosphorylation, they homo- and heterodimerize and tetramerize (Vinkemeier et al., 1996; John et al., 1999; Zhang and Darnell, 2001). STATs are transported into the nucleus via importins (reviewed by (Levy and Darnell, 2002) where they bind consensus SIE (sis-inducible element), GAS (gamma activated sequence), or ISRE (interferon stimulated regulating element) sequences. Other mechanisms of STAT activation include phosphorylation by non-receptor tyrosine kinases such as Src, direct or indirect phosphorylation by receptors with intrinsic tyrosine kinase activity (i.e. EGF, PDGF, and FGF receptors), and activation by G-protein coupled receptors (GPCRs; reviewed by (Lim and Cao, 2006). Signaling is turned off when STATs are dephosphorylated in the nucleus by phosphatases (Haspel and Darnell, 1999), and exported back to the cytoplasm by nuclear export signals present within STATs' DNA binding domains (McBride et al., 2000; Bhattacharya and Schindler, 2003; Meyer et al., 2003). Proteins that inhibit activated STATs (PIAS) negatively regulate STATs either by interacting with their phosphorylated tyrosines and blocking DNA binding or by other mechanisms as yet unknown (Chung et al., 1997; Shuai, 2000; Arora et al., 2003; Wormald and Hilton, 2004). Arginine methylation of STATs disrupts their ability to interact with PIAS, thus increasing their ability to affect transcription (Mowen et al., 2001). Additionally, suppressor of cytokine signaling (SOCS) proteins are able to bind to JAK sites and inhibit additional STAT activation (Krebs and Hilton, 2001).

STAT3 Expression in the Nervous System

STAT3 is probably the best studied family member in the nervous system. STAT3 is expressed in the cortex, striatum, basal forebrain, and hippocampus as early as embryonic day 14 (E14) through adult (De-Fraja et al., 1998) in both neurons and glia (Gautron et al., 2006). STATs can be activated by IL-6, CNTF, LIF, G-CSF, EPO, NGF, PDGF, estradiol, and IGF-I, correlating with increased survival and neuroprotection (reviewed by (Dziennis and Alkayed, 2008). STAT3 knockouts are embryonic lethal (Takeda et al., 1997), necessitating targeted knockout to specific populations to determine its function. During development, STAT3 knockout or constitutive activation can affect motoneuron pathfinding in zebrafish (Conway, 2006). In the adult, there are low basal levels of STAT3 expressed in neurons, except in a small population of neurons including areas of neurogenesis, and after trauma such as ischemia or axotomy (reviewed by (Dziennis and Alkayed, 2008).

Role of STAT3 in Neurite Growth and Regeneration

What is STAT3's effect on regeneration? Following peripheral facial nerve axotomy, there is a rapid increase in cytoplasmic STAT3 phosphorylation and translocation into the nucleus which has been shown to remain up to 3 months in regenerating neurons (Schwaiger et al., 2000). This was not seen after injury in neurons that are unable to regenerate, suggesting that the presence of phosphorylated nuclear STAT3 may be a necessary part of peripheral nerve regeneration (Schwaiger et al., 2000).

STAT3 has also been implicated in a conditioning lesion paradigm of regeneration. After sciatic nerve injury, phosphorylated STAT3 was increased from 6 hours through 1 month, whereas after a central dorsal column injury, there was no increase in phosphorylated STAT3. Application of a JAK/STAT inhibitor for 4 weeks at the lesion site not only resulted in a decrease in phospho-STAT3 in DRG neurons, but also in reduced expression of the regeneration-associated protein GAP-43. Following a peripheral nerve conditioning lesion concurrent with application of JAK/STAT inhibitors, in vitro DRG dissociation revealed that while there was no difference in the number of cells with neurites, there was a significant decrease in neurite length after inhibitor treatment. To test this in vivo, the same

peripheral crush with concurrent JAK/STAT inhibition was followed by a dorsal column crush and a month more of JAK/STAT inhibitor treatment at the lesion site. The regenerative effect of the conditioning lesion was abolished in the presence of the JAK/STAT inhibitors (Qiu et al., 2005). Taken together, these data suggest a role for STAT3 in the conditioning effect of the peripheral lesion. This is similar to the results discussed above, showing a role for cAMP and CREB in this same conditioning lesion effect (Gao et al., 2004), suggesting that there may be cross-talk between these two signaling pathways in this system.

IL-6 and LIF are two of the many upstream signals that can lead to downstream activation of STAT3. When LIF was knocked out and a conditioning lesion paradigm of regeneration studied, regeneration was impaired (Cafferty et al., 2001), with similar results in the same paradigm in IL-6 knockout mice (Cafferty et al., 2004). A similar study using IL-6 knockouts, however, was unable to replicate these results, though they did demonstrate that IL-6 was sufficient, but not necessary, to imitate the previously mentioned effects of cAMP in the conditioning lesion injury (Cao et al., 2006). Thus, while the upstream players in the STAT3 pathway that are responsible for conditioning injury-induced regeneration are still unclear, the data strongly suggest that downstream STAT3 activation plays an important role.

Is there a similar role in the CNS? In the eye, a lens injury concurrent with optic nerve crush increases the ability of RGCs to grow their axons in vitro and regenerate in vivo (Fischer et al., 2000; Leon et al., 2000; Fischer et al., 2001). Lens injury increases CNTF levels in retinal astrocytes, which corresponded with an increase in phospho-STAT3 in RGCs. Application of antibodies against CNTF or JAK inhibitor treatment after lens injury and optic nerve crush reduced not only the levels of phospho-STAT3 in RGCs, but also reduced axon growth from retinal explants. This suggests that most of the effect of lens injury may be due to JAK/STAT signaling. Interestingly, STAT3 remained activated over the entire 2 week observation period (Muller et al., 2007). In concordance with these data, in microarray analyses of genes upregulated by lens injury and optic nerve crush, two of the highest expressed genes are both targets of STAT3 (Fischer et al., 2004). STAT3 has also been shown to be important for neurite growth outside of the conditioning lesion/treatment phenomenon. In vitro knockdown of STAT3 in hippocampal neurons led to decreased BDNF-induced neurite growth (Ng et al., 2006). Therefore STAT3 may have a global function in promoting neurite growth in multiple systems.

Other treatments using CNTF have been performed to increase axon regeneration in RGCs (Harvey, 2007). While not directly showing a dependence on STAT3, these results suggest that CNTF application followed by increased activated STAT3 may increase axon regeneration in RGCs. Importantly, knocking out the suppressor of cytokine signaling-3 (SOCS-3) greatly enhances regeneration, suggesting that a break on JAK/STAT signaling normally limits RGCs' regenerative capacity (Smith et al., 2009). Thus STAT3 is expressed in regenerating neurons, and plays an important role in the pre-conditioning lesion and lens injury models of axon regeneration in the PNS and CNS, respectively.

STAT3's Subcellular Localization

STAT3 activation after sciatic nerve injury occurs in axons within 15 minutes of lesioning, leading to retrograde signaling to the nucleus (Lee et al., 2004). In compartmentalized cultures of sympathetic neurons, LIF treatment at the end of axons triggers phosphorylation of local STAT3, as well as translocalization of phospho-STAT3 to the nucleus, though this translocation was not necessary for retrograde signaling. Retrograde transport and signaling is carried by signaling endosomes containing LIF/gp130/LIFR/JAK that are retrogradely transported to the cell body to activate nuclear STAT3 (O'Brien and Nathanson, 2007).

Phosphorylated STAT3 has also been found in focal adhesions and pseudopodial protrusions (Silver et al., 2004; Jia et al., 2005). Additionally, STAT3 has been found in post-synaptic densities (PSD) in P21 rat brain, where it can be tyrosine phosphorylated by local JAK2. Surprisingly, this phosphorylation did not release STAT3 from the PSD (Murata et al., 2000). Therefore, it is unclear whether activated STAT3 in injured axons acts only as a retrograde signal, or also in axon growth or related functions.

Effects of Post-Translational Modifications on Function

Other than phosphorylation, additional post-translational modifications include acetylation by co-activators such as p300/CBP, which increases STATs' transcriptional efficacy, and deacetylation by histone deacetylases (HDACs; (McDonald and Reich, 1999; Paulson et al., 1999; Shankaranarayanan et al., 2001; Wang et al., 2005; Yuan et al., 2005). Some STATs can also be sumoylated or ubiquitinated, though this has not yet been determined for all of the STAT family members (reviewed by (Lim and Cao, 2006). Serine phosphorylation can affect STATs differently, such that it can enhance DNA binding and transcriptional activation, allow binding to the co-activator p300, decrease transcriptional activation or the rate of tyrosine phosphorylation, or enhance neurite growth (Decker and Kovarik, 2000; Schuringa et al., 2001; Ng et al., 2006). Interestingly, the serine phosphorylated version of STAT3 has been shown to be induced after spinal cord injury (Tsai et al., 2007).

NFATc

The nuclear factor of activated T cells (NFAT) transcription factor family consists of 5 members, including the NFATc1-4 proteins, which respond to changes in calcium through calcineurin, and NFAT5, which though somewhat structurally homologous, does not respond to changes in calcium but to changes in tonicity. All NFATs possess a Rel DNA-binding domain similar to the NFκB/Rel family (reviewed in (Hogan et al., 2003). In 2000, the official naming of the NFATs was revised and standardized by the Hugo Nomenclature Committee, replacing the multiple names previously used in the literature.

NFATc1-4 (hereafter simply called "NFAT") respond to increases in intracellular calcium, mediated in neurons by L-type calcium channels (Graef et al., 1999). Calcium increases lead to activation of the phosphatase calcineurin which can dephosphorylate NFATs, thereby activating them by revealing their nuclear localization signal (NLS). NFATs can be regulated by inhibition of calcineurin (Coghlan et al., 1995; Miyazaki et al., 1996; Lai et al., 1998; Sun et al., 1998; Lin et al., 1999; Fuentes et al., 2000; Rothermel et al., 2000), or by phosphorylation by GSK-3 (Beals et al., 1997; Neal and Clipstone, 2001; Sheridan et al., 2002), DYRK1A or 2 (dual-specificity tyrosine-phosphorylation regulated kinase) (Gwack et al., 2006), JNK (Chow et al., 1997), p38 MAPK (Gomez del Arco et al., 2000), and casein kinase in combination with MEKK1 (Zhu et al., 1998). Besides phosphorylation, studies have shown that sumoylation of NFATc2 is important for nuclear anchorage and for its ability to regulate transcription (Terui et al., 2004). NGF, BDNF, and substance P have been found to trigger NFAT-dependent transcription in neurons (Graef et al., 2003; Groth and Mermelstein, 2003; Seybold et al., 2006; Groth et al., 2007). In neurons, NFAT is also activated in response to synaptic activity or depolarization (Graef et al., 1999).

As their own DNA binding is relatively weak, NFATs require a partner to bind DNA (Flanagan et al., 1991; Wolfe et al., 1997; Chen et al., 1998; Zhou et al., 1998) and provide substrate specificity (for review, see (Crabtree and Olson, 2002). For this reason, NFATs are often described as "coincidence detectors" and "signal integrators" (Graef et al., 2001). They can interact with STAT3 (Manukyan et al, 2009), c-Jun (Behrens et al, 2001), CREB and ATF3 (Kim et al, 2006).

NFAT Expression in the Nervous System

NFAT is highly expressed in the brain (Plyte et al., 2001; Wilkins et al., 2004) and in the spinal cord (Seybold et al., 2006; Groth et al., 2007). In the brain, NFATc2 expression increases through development, from E10 to adulthood, NFATc3 expression remains low throughout development, and NFATc4 expression is highest during the period from E10 to P1 (Nguyen et al., 2009), suggesting that differences in expression of these family members may be a clue to different roles they perform in the brain. Splice variants of each of these family members result in 8 proteins from NFATc1, 6 from each of NFATc2 and c3, and up to 24 isoforms of NFATc4, in humans, which could add to the complexity with which the NFAT family acts (Vihma et al., 2008). It is very likely that these family members function with some redundancy, as single NFATc knockout mice appear normal, whereas combinations of NFATc3/c4 and NFATc2/3/4 lead to sensory axon projection defects (Graef et al., 2003). Additionally, there may be cross-regulation within the family, as NFATc2 levels in NFATc4 knockout mice were very different from wildtype (Nguyen et al., 2009).

Role of NFAT in Neurite Growth and Regeneration

Axon growth during development requires at least some NFATc signaling, as removal of NFATc2, c3, and c4 results in sensory neuron axon projection defects in vivo (Graef et al., 2003). In addition, spinal cord explants from these mutant mice were unable to extend axons in response to netrin (Graef et al., 2003). Interestingly, NFATc4 was shown to have a repressive role in the CNS, opposite of other studies, repressing GAP-43 and CAP-23 expression in the absence of neurotrophin signaling (Nguyen et al., 2009). Thus, NFATs respond to neurotrophins, netrins and electrical activity in neurons to regulate neurite growth, and future studies focused on binding partners and downstream gene targets may more completely define the role of NFATs in neurons.

NF-κB

NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells) is an inducible transcription factor dimer made up of 5 possible subunits, bound as homo- or heterodimers: RelA/p65, c-Rel, RelB, p50 and p52, with the last 2 proteolytically cleaved from larger precursors. p65, c-Rel and RelB have a transcription activation domain (TAD) which allows them to activate transcription, whereas p50 and p52 depend on dimerization with them to positively regulate transcription. Each monomer has an N-terminal Rel homology domain, similar to NFATs, responsible for DNA binding, dimerization, nuclear binding, and nuclear localization (reviewed by (Hoffmann et al., 2006). NF-κB is regulated by the Inhibitor of κB (IκB) family of proteins, which binds to the transcription factor dimer, keeping it in the cytoplasm. Dissociation or proteasomal degradation of IκB reveals NFκB's nuclear localization sequence (NLS), allowing it to translocate to the nucleus and affect gene transcription by binding κB sequences in promoters and enhancers (reviewed by (Perkins, 2007; Vallabhapurapu and Karin, 2009). There are many signals that can activate NFκB signaling, including growth factors, neurotransmitters, cytokines, electrical activity and synaptic transmission, and inhibit NFκB signaling, including TGFβ, GSK-3β, glucocorticoids, IL-4, and IL-10 (reviewed by (Kaltschmidt et al., 2005; Mattson, 2005).

Expression of NFκB in the Nervous System

The most common NFκB dimer in the nervous system is p50:p65, but other dimers including p65:c-Rel and p50:c-Rel are detected in the brain as early as E17 (reviewed by (Kaltschmidt et al., 2005). In the brain, NFκB plays roles in cell survival, synaptic plasticity, learning and memory, and is activated in stroke, seizures, traumatic brain injury, Alzheimers, Huntingtons and Parkinsons diseases (reviewed by (Mattson, 2005; Romano et

al., 2006). Reporter mice driven by various NFκB-dependent DNA elements also suggest that the majority of NFκB activity in the brain begins after birth, in the cerebellum around P6, and in hippocampus and cortex around P15, and into adulthood in multiple areas of the brain (Schmidt-Ullrich et al., 1996). Other groups have shown NFκB activity by E13 in multiple brain regions and in the olfactory lobes through adulthood (Bhakar et al., 2002). In the adult PNS, activated NFκB is present in naïve DRG and spinal cord, and is significantly upregulated after peripheral nerve crush in both areas (Ma and Bisby, 1998; Fernyhough et al., 2005; Pollock et al., 2005).

NFκB's Subcellular Localization

What is the localization of NFκB in neurons? In embryonic hippocampal cultures, glutamate receptor activation or depolarization can lead to relocalization of cytoplasmic NFκB to the nucleus. p65 fusion experiments revealed that p65 in the neurites can retrogradely travel to the nucleus after stimulation with glutamate, kainate or KCl, and this requires its NLS. The addition of high levels of IκBα lead to a cytoplasmic accumulation of NFκB (Wellmann et al., 2001). This suggests that NFκB can respond to a stimulus in neurites and retrogradely travel to the nucleus to affect gene transcription.

Role of NFκB in Neurite Growth and Regeneration

Does NFκB play a role in neurite growth? Inhibition of NFκB DNA binding by preventing IκB-α mediated release of NFκB transcription dimers leads to inhibition of neurite growth in nodose sensory neurons without affecting survival (Gutierrez et al., 2005). Interestingly, this effect was seen only in neurons between E18 and P1, suggesting a specific developmental window where NFκB is required for elongation and arborization. This suggests that NFκB activation can affect neurite growth, however, it may function differentially at different times in development, or as discussed below, in specific cell types.

Similar results were seen with CNTF supplemented sensory neuron cultures, where inhibition of NFκB DNA binding decreased CNTF-induced neurite growth and branching, although this effect was mediated through a non-classical pathway targeting the phosphorylation of Tyr-42 of IκBα by CNTF-induced signaling through spleen tyrosine kinase (SYK) (Gallagher et al., 2007). There was no effect on survival in any treatment. Thus, in sensory neurons, CNTF functions to activate SYK which phosphorylates the Tyr-42 of IκBα to release NFκB for translocation to the nucleus, leading to transcriptional changes that are essential to CNTF-mediated increases in neurite growth and branching (Gallagher et al., 2007).

NFκB is also the downstream modulator of neurite growth for fas apoptosis inhibitory molecule (FAIM) signaling (Sole et al., 2004). In multiple neuronal types, overexpression of FAIM-S (short isoform) not only promoted NFκB activation, but also increased neurite length (Sole et al., 2004). Blocking NFκB activation prevented the increase of neurite growth seen with FAIM-S overexpression. Knockdown of FAIM-S decreased both neurite length and branching. Whereas overexpression of FAIM-S increased growth in WT cortical neurons, overexpression in a p65-/- background resulted in neurite growth more similar to controls. These data suggest that FAIM-induced changes in neurite growth rely on NFκB-driven changes in transcription.

Effects of Post-Translational Modifications on Function

Phosphorylation of p65 can increase or decrease neurite growth of primary neurons. Blocking NFκB signaling in cultured sympathetic neurons did not affect neurite growth, in contrast to what was shown with sensory neurons (Gutierrez et al., 2008). Interestingly, overexpression of the p50:p65 dimer decreased neurite growth in sympathetic neurons,

whereas in sensory neurons it increased growth (Gutierrez et al., 2008). In both situations, however, NFκB -dependent gene transcription was increased. Why does this overexpression of NFκB function differently in different types of neurons? One difference between the neuronal types is that IKKβ activation was higher in sympathetic neurons and virtually undetectable in sensory neurons (Gutierrez et al., 2008). IKKβ can phosphorylate p65 on Ser- 536 (Sakurai et al., 1999), and in agreement, p65 was constitutively phosphorylated in sympathetic neurons, but not in sensory neurons. Indeed, the overexpression of the WT versions of p50:p65 led to increased phospho-p65 in sympathetic neurons, but not sensory neurons (Gutierrez et al., 2008). Overexpression of the p50:phosphomimic Ser-536-p65 in sensory neurons decreases neurite growth, whereas overexpression of wildtype p50:p65 increases growth (Gutierrez et al., 2008). Phospho-Ser-536-p65 can regulate specific gene targets (Buss et al., 2004; Sasaki et al., 2005), suggesting these genes could reveal molecular mechanisms behind phenotype changes in neurite growth both in NFκB signaling, and in general. Thus, in neurons with active IKKβ and thus phosphorylated p65, there is reduced neurite growth, and in neurons without this IKKβ activity, the unphosphorylated p65 can lead to enhanced neurite growth, suggesting a switch that can control neurite growth depending on a post-translational modification (Gutierrez et al., 2008).

An interesting developmental switch occurs in the mechanisms of BDNF-promoted NFκB signaling in sensory neurons at birth. Before birth, cultured sensory neurons respond to BDNF through TrkB with an increase in Src-mediated tyrosine phosphorylation of IκBα, leading to dissociation, though not proteasome-mediated degradation, from the NFκB dimer and an increase in NFκB signaling by a dephosphorylated p65, and thus an increase in neurite growth and branching. Overexpression of a phosphomimic p65 reduces neurite growth in these E17 sensory neurons. Thus at E17, BDNF enhances NFκB activation and promotes the dephosphorylation of p65 (Gavalda et al., 2009). After birth, however, BDNF-promoted NFκB activation is constitutive and not further increased, IkBα is not tyrosine-phosphorylated (Gavalda et al., 2009), though serine phosphorylation is still necessary (Gutierrez et al., 2005). After birth, inhibition of the proteasomal machinery, not important to neurite growth at E17, leads to decreases in neurite growth. p65 Ser-536 phosphorylation is also unaffected by BDNF application after birth, and its low basal levels remain unchanged (Gavalda et al., 2009). These studies suggest that the mechanism behind BDNF-promoted NFκB signaling and neurite growth changes during development.

Mechanisms of Transcriptional Control

Although the gene targets behind NFκB's effects on neurite growth have not been identified, several gene targets of NFκB have been identified in other systems (Pahl, 1999). Some of these targets are cell adhesion molecules such as NCAM (Simpson and Morris, 2000), tenascin C (Mettouchi et al., 1997), and β1 integrin (Wang et al., 2003). In neurons, genes for Bcl-2, MnSOD, glutamate receptor subunits, BDNF, and calcium regulating proteins are activated by NFκB transcription (reviewed by (Mattson, 2005). In addition, all of the IκB proteins are targets of NFκB signaling (reviewed by (Hoffmann et al., 2006). Understanding the transcriptional outcome of NFκB signaling in the context of different post-translational modification states or developmental periods is necessary to further unravel the mechanisms behind neurite growth and regeneration.

NFκB Interactions with Other Signaling Pathways

NFκB can interact with many transcription factors in other signaling pathways, including the Jun, ATF, CREB and Fos transcription factor families. In addition, STAT3 can induce the alternative NFκB pathway, and can bind DNA in a complex with p52, the proteolytic product of p100, to induce transcription (reviewed by (Perkins, 2007). p53 can also interact with p52, recruiting it to p53-regulated promoters for both interaction and recruitment of co-

repressors and co-activators to regulate p53's target genes (Schumm et al., 2006). NFκB can compete for the same co-activators: for example, p53 and NFκB compete for binding to CBP (reviewed by (Perkins, 2007). IKKα can phosphorylate CBP at Ser-1382 and Ser-1386 in response to TNFα stimulation, resulting in a shift of CBP from p53 to phosphorylated p65, switching CBP recruitment from p53- to NFκB-dependent promoters. This phosphorylation of CBP also increases its intrinsic HAT activity, resulting in its ability to acetylate histone tails and increase transcriptional activation (Huang et al., 2007).

SOX11

SRY-box containing gene 11 (Sox11) is one of more than 20 members of the Sox transcription factor family, with homology to the high mobility group (HMG) domain of the SRY gene and the ability to activate or repress gene transcription. The family members can be separated into subfamilies on the basis of their homology in the DNA-binding HMG domain, with Sox11, -4 and -12 as part of Group C (Prior and Walter, 1996; Kamachi et al., 2000). The HMG domain of SOX family members is not only responsible for DNA binding, but also for interactions with other transcription factors, as well as containing signals for nuclear import, and in a few Sox proteins, nuclear export (reviewed in (Wilson and Koopman, 2002). Sox proteins bind a 6 base pair DNA consensus sequence. Sox factors regulate different genes in different cells through recruitment of partner proteins that bind different DNA sequences flanking the Sox binding site. Most Sox transcription factors possess an activation domain in their C terminus, but bind to DNA with low affinity. DNA-binding co-factors increase Sox-DNA binding strength and thus their ability to affect transcription (reviewed in (Kamachi et al., 2000). For example, Sox2 binds to the Fgf4 enhancer, though it cannot activate Fgf4 expression alone. Oct3/4 also cannot elicit transcription alone, but Oct3/4 binding next to Sox2 leads to transcriptional activation, dependent on close proximity between these binding sites (Yuan et al., 1995; Ambrosetti et al., 1997). Sox11 may also partner with Brn1 or -2 to regulate transcription (Kuhlbrodt et al., 1998; Tanaka et al., 2004).

Mechanisms of Transcriptional Control

A few relevant gene targets of Sox 11 have been identified. For example, Sox11 drives expression of neurite growth-associated genes beta-III tubulin and MAP2 (Bergsland et al., 2006) and actin-related protein complex 3 (Arpc3) (Jankowski et al., 2006), but overall there has been limited study of Sox11 targets relevant to axon growth to date.

Effects of Post-Translational Modifications on Function

Sox proteins can be affected by post-translational modifications, though these have not yet been well characterized. Many Sox factors have putative phosphorylation sites, however, only Sox9 has been shown to be phosphorylated, leading to an enhancement of its transcriptional and DNA binding activities (Huang et al., 2000; Huang et al., 2001). In addition, other Sox proteins can be ubiquitinated and sumoylated in vitro, though there has been no reports of relevant post-translational modifications of Sox11 to date (reviewed in (Lefebvre et al., 2007).

Sox11 Expression in the Nervous System

Sox11's initial characterization was through its involvement in neuronal differentiation and development (Uwanogho et al., 1995; Hargrave et al., 1997; Rex et al., 1998; Hyodo-Miura et al., 2002). In the PNS, Sox11 is highly expressed in embryonic and regenerating DRGs and at low levels in adult neurons (Hargrave et al., 1997; Tanabe et al., 2003; Jankowski et al., 2006). Sox11 is also expressed in the developing CNS (Uwanogho et al., 1995; Hargrave et al., 1997; Rimini et al., 1999; Cheung et al., 2000; de Martino et al., 2000), and is

downregulated during development in RGCs (Wang et al., 2007). After optic nerve injury in the regenerating zebrafish model, Sox11a and b were strongly upregulated (8 fold) in RGCs as detected in microarray data (Veldman et al., 2007). Sox11 expression can also be upregulated after neuronal depolarization in both embryonic cortical neurons in vitro and adult brain in vivo (Sun et al., 2005). Thus, Sox11 expression is highest during periods of axon growth and regeneration.

Role of Sox11 in Neurite Growth and Regeneration

In Neuro2a cells, Sox11 levels dramatically increased with the number of cells extending neurites, suggesting a correlation between Sox11 and neurite outgrowth. After DRG injury, when regenerative growth programs are initiated, Sox11 expression is highly increased (Tanabe et al., 2003; Jankowski et al., 2006; Jankowski et al., 2009), but expression levels are only slightly increased after central nerve injury, where regeneration is not observed (Jankowski et al., 2009). In the PNS, in vitro knockdown of Sox11 in DRG neurons reduces neurite growth, but it also increases apoptosis, making interpretation of these data more complicated (Jankowski et al., 2006). Similarly, in the PNS in vivo after saphenous nerve injury, knockdown of Sox11 results in a decrease in axon regeneration a week after crush (Jankowski et al., 2009). In CNS regeneration, knockdown of Sox11a/b in zebrafish retinal explants had no effect on axon outgrowth (Veldman et al., 2007), although there may compensation by highly homologous family members.

Interestingly, Sox11 may work with other transcription factors to affect neurite growth and regeneration. In vivo, Sox11 knockdown reduced the elevation of ATF3 following PNS injury, whereas in vitro, this knockdown led to a decrease in ATF3 expression. ATF3 knockdown, however, did not affect Sox11 levels, suggesting Sox11 acts upstream of ATF3 to positively modulate its expression after peripheral nerve injury (Jankowski et al., 2009).

SnoN AND E47

SnoN is a member of the evolutionarily conserved ski/sno/dac gene family. The majority of the members of the ski/sno/dac superfamily possess a highly homologous ski/sno/dac domain as well as a SAND domain which does not directly bind DNA, but creates an interaction loop through its zinc finger motif allowing for structural stability. SnoN and its earlier discovered predecessor Ski, make up one subgroup of this family (reviewed by (Pot and Bonni, 2008). Their N-termini are highly homologous, and their C termini mediate homo- or heterodimerization (Cohen et al., 1999; Luo, 2004). There are 4 alternatively spliced forms of the sno gene, with SnoN being the major isoform (reviewed in (Pot and Bonni, 2008). SnoN and Ski have multiple functions in cell proliferation and differentiation (reviewed in (Pot and Bonni, 2008).

SnoN's repressor function in TGFβ signaling has been well-characterized. SnoN can repress TGFβ target genes through recruitment by Smads to Smad-binding elements in TGFβ promoters. It complexes with multiple repressive proteins including N-CoR, HDAC and mSin3 to repress these target genes. In addition, it can inhibit the interaction of Smads with the transcriptional co-activator p300/CBP (reviewed in (Luo, 2004). Upon TGFβ pathway activation, SnoN can become targeted for destruction by ubiquitination, thus relieving the repression on the TGFβ target genes (Stroschein et al., 1999). SnoN contains a D-box motif which allows it to be targeted for destruction. Its imperfect D box however, decreases its affinity for the Cdh1/APC complex, thus requiring additional stability through Smad binding for effective ubiquitination (Stroschein et al., 2001). SnoN proteosomal degradation is regulated through the E3 ubiquitin ligases anaphase promoting complex (APC), SMAD-specific E3 ubiquitin protein ligase 2 (Smurf2) or Arkadia (Bonni et al., 2001; Stroschein et al., 2001; Wan et al., 2001; Levy et al., 2007; Nagano et al., 2007). It has also been

suggested that phosphorylation by TAK1 can prime SnoN for degradation (Kajino et al., 2007).

Role of SnoN in Neurite Growth and Regeneration

Recent studies have found an important role for APC mediated degradation of SnoN in regulating neurite growth and regeneration. Normally, APC is targeted to its substrate by its co-activator protein Cdh1 and regulates cell cycle transitions by ubiquitinating its targets, leading to their degradation (Kim and Bonni, 2007). Using cerebellar granule neurons, Cdh1/APC was found to inhibit axon growth (Konishi et al., 2004), partially through its interaction with SnoN (Stegmuller et al., 2006). In neurons, Cdh1 interacts with SnoN in the nucleus, targeting it for degradation. Knockdown of SnoN mimics this effect, decreasing neurite growth. When SnoN knockdown is combined with the axon growth-promoting effect of Cdh1 knockdown, there is still a decrease in neurite growth, suggesting that SnoN is downstream of Cdh1 in regulating neurite growth. SnoN is expressed in granule neurons in the developing cerebellum, and its knockdown in the cerebellum in vivo impairs development of granule neuron parallel fibers, suggesting an important role for SnoN on axonal elongation and patterning in cerebellar granule neurons. SnoN is also expressed in cultured hippocampal and cortical neurons, and its knockdown results in decreased axon growth, suggesting that SnoN may function in multiple cell types to control axon growth ability (Stegmuller et al., 2006). In vivo, SnoN expression decreases in the adult brain, correlating with the loss of regenerative ability in adult CNS neurons (Stegmuller et al., 2008).

In a parallel pathway, TGFβ receptor type I recruits Smads -2 and -3, activating them by phosphorylation, at which time they complex with a regulatory Smad and enter the nucleus (ten Dijke and Hill, 2004). SnoN can be recruited by TGFβ signaling through Smad2/3 (reviewed in (Pot and Bonni, 2008), and Smad2 can directly interact with SnoN (Stegmuller et al., 2008). TGFβ signaling can activate Smad 2/3 to recruit SnoN to the Cdh1/APC complex, leading to its subsequent ubiquitination and degradation (Stegmuller et al., 2008).

Mechanisms of Transcriptional Control - SnoN

What are SnoN's gene targets? SnoN has primarily been shown to be a repressor, however, gene profiling revealed that SnoN knockdown results in many downregulated genes, suggesting a role for SnoN as an activator of transcription in neurons (Ikeuchi et al., 2009). The transcriptional co-activator p300 binds SnoN and its knockdown decreases neurite growth, similar to SnoN knockdown. Consistent with the TGFβ signaling pathway outlined above, many known TGFβ signaling target genes are regulated by SnoN. An actin-binding protein, ccd1, is transcribed in response to SnoN in cerebellar granule neurons (Ikeuchi et al., 2009), activates JNK signaling in neurons (Ikeuchi et al., 2009), and is required for axon growth, suggesting that SnoN is functioning through ccd1 to enhance neurite growth. In vivo knockdown of ccd1 in cerebellar granule neurons resulted in decreased numbers of parallel fiber axons, a phenotype similar to that SnoN knockdown, further supporting a role for ccd1 as a target whose regulation is required for SnoN-mediated increases in axon growth ability (Ikeuchi et al., 2009). Thus a pathway from Cdh1/APC through SnoN modified by TGFβ signaling and dependent on downstream ccd1 expression regulates axon growth in cerebellar granule neurons.

Another target of Cdh1/APC is the inhibitor of DNA binding 2 (Id2), which can inhibit the activity of basic-helix-loop-helix (bHLH) transcription factors. The E2A gene encodes two bHLH transcription factors, E12 and E47, which can homo- or heterodimerize with other tissue-specific bHLH regulators, who through their cooperation or inhibition determine positive or negative regulation of gene expression. Their levels can be regulated by Id

proteins, the ubiquitin-proteasomal pathway, and phosphorylation (Slattery et al., 2008). Cdh1/APC targets Id2 for degradation which leads to an increase in the bHLH transcription factor, E47. Expression of a degradation-resistant Id2 leads to increased axon growth. If Cdh1 is knocked down concurrent with E47 overexpression, there is still a decrease in axon growth. This suggests that Cdh1/APC can also modulate transcriptional changes through degradation of Id2 and an upregulation in bHLH proteins. Interestingly, E47 can increase expression of multiple proteins that are inhibitory to axonal growth, such as NogoR, Notch1, Unc5A, Jagged2, and Sema3F (Lasorella et al., 2006). Together, these studies have been well characterized in cerebellar granule neurons, and it will be interesting to study the functions of these transcription factors after CNS or PNS injury in vivo.

KLFs

The Krüppel-like factor (KLF) family of 17 transcription factors all contains 3 highly homologous Cys_2/His_2-type zinc fingers on their C termini with highly conserved regions between them. They bind DNA at CACCC/GC/GT boxes, which are highly represented throughout regulatory regions in the genome. They are often grouped with the Sp (specificity protein) family, though the KLF family is distinguished by the absence of the Sp family's Buttonhead (BTD) box 5’ to the zinc fingers (Suske et al., 2005). Many KLFs have been thoroughly studied in cancer, and can play roles in cell cycle, proliferation, and cell death (Black et al., 2001). Little is known, however, about the expression or function of the 17 KLFs in the mammalian nervous system.

KLF domains important in DNA binding and co-factor recruitment are critical to their function. For example, KLF9 can activate or repress transcription through recruitment of the co-repressor Sin3A (Imataka et al., 1992; Zhang et al., 2001), and KLF4 has both activator and repressor capabilities, depending on interactions with the transcriptional co-repressors such as CtBP1 (Liu et al., 2009). KLF15 can repress the rhodopsin promoter, however, deletion of its N terminus results in a switch to a transcriptional activator (Otteson et al., 2004).

KLFs or KLF activity may be regulated by a variety of signaling pathways. For example, KLF9's expression is positively regulated by binding of T3 receptor-retinoid X receptor heterodimers to the T3 response element (T3RE) in the 5’ flanking region of the KLF9 gene (Denver and Williamson, 2009), by corticosterone (Bonett et al., 2009), and by activity (Lin et al., 2008; Scobie et al., 2009). KLF4 is upregulated by NMDA or AMPA treatment in cortical neuron cultures.

KLFs Expression in the Nervous System

KLFs are expressed ubiquitously throughout other body tissues, and it is typical for single cells to express multiple KLFs. There are few systematic examinations of KLF expression in the nervous system, but a number of KLFs are expressed. For example, RGCs express 15 of 17 KLFs, and the expression of many of these factors was developmentally regulated, and could be correlated with their effect on neurite growth after overexpression (see below) (Moore et al., 2009). KLF9 is a thyroid hormone (T3)-regulated transcription factor whose expression in the brain begins postnatally (Denver et al., 1999; Martel et al., 2002; Morita et al., 2003), and is developmentally regulated, increasing after birth and maintaining higher expression into adulthood (Denver et al., 1999), similar to the pattern of developmental regulation seen in RGCs (Moore et al., 2009). KLF16 is expressed in brain in embryos and adult animals (Hwang et al., 2001; D'Souza et al., 2002). KLF15 is expressed in various parts of the brain, and in the retina in the inner nuclear layer and ganglion cell layer (Otteson et al., 2004). In purified RGCs of the ganglion cell layer, its expression is upregulated during development (Moore et al., 2009). KLF12 is expressed in the brain in a complex pattern,

with the highest levels shortly after birth (Imhof et al., 1999). KLF5 is expressed in the human prefrontal cortex, and in the granular and pyramidal cells of the hippocampus. KLF5 is downregulated in the prefrontal cortex in schizophrenia patients, and a polymorphism of KLF5 is associated with schizophrenia (Yanagi et al., 2008). Thus a number of KLFs are expressed throughout the nervous system, although more comprehensive studies are certainly warranted.

Role of KLFs in in Neurite Growth and Regeneration

Recently, our lab has demonstrated a role for KLFs in axon regeneration both in vitro and in vivo. CNS neurons such as RGCs lose their intrinsic axon growth ability as they age (Goldberg et al., 2002). To identify genes that could be involved in this loss, we performed a screen of candidate genes whose expression was developmentally regulated in RGCs, and identified KLFs as potent regulators of neurite growth in RGCs, hippocampal, and cortical neurons (Moore et al., 2009; Blackmore et al., 2010). KLF4 knockout in RGCs leads to increased neurite growth in vitro, and increased regeneration in vivo. Additionally, multiple developmentally regulated KLF family members can differentially regulate growth in both cortical neurons and RGCs, further suggesting a transcriptional network that controls axon growth and regeneration (Moore et al., 2009). A number of KLFs which decreased developmentally (e.g. KLF6, KLF7), when overexpressed increased neurite growth, whereas some KLFs which increased postnatally (e.g. KLF4, KLF9), when overexpressed decreased neurite growth. In addition, their ability to affect neurite growth (positively, negatively, or neutrally) could be correlated with their structural subgroups within the KLF family.

Others have also documented the ability of KLFs to regulate neurite growth. For example, KLF6 and -7 have been identified as growth enhancers in other studies. KLF7 is highly expressed in both the PNS and CNS throughout development (Laub et al., 2001; Lei et al., 2001), and KLF6 has also been shown to be expressed in the developing nervous system (Laub et al., 2001), and in the adult, is present in neurons, endothelial cells and neuronal progenitors in the forebrain (Jeong et al., 2009). KLF7 knockout results in deficits in axon growth and pathfinding in the olfactory system, retina, and brain (Laub et al., 2005; Laub et al., 2006). In retinal explants in zebrafish, KLF7 was found, together with KLF6, to be necessary for axon growth (Veldman et al., 2007).

There is variability in the reported effects of KLF9 on neurite growth. In cell lines, overexpression of KLF9 leads to an increase in the number of cells extending neurites as well as increasing the number and length of the neurites (Denver et al., 1999). In embryonic cortical neurons and small acetylcholinesterase (AChE) expressing cells, knockdown of KLF9 decreases neurite branching without affecting elongation(Cayrou et al., 2002). In contrast, in embryonic and postnatal RGCs, and young postnatal cortical neurons supplemented with T3, KLF9 overexpression decreases neurite growth, suggesting possible differences for this factor in different cell and neuronal types (Moore et al., 2009). Similarly, KLF9 knockout mice do not demonstrate defects in axon targeting and dendrite length in the hippocampus (Scobie et al., 2009), although there may be a slight deficit in Purkinje cell dendrites (Morita et al., 2003).

Mechanisms of KLF Regulation

KLFs can cross-compensate for each other throughout the body, including in neurite growth regulation. For example, KLF6 and KLF7 were able to compensate for each other in their ability to affect axon growth (Veldman et al., 2007). In primary neurons in culture, overexpression combinations of suppressors and enhancers led to the suppressors dominating, and decreased neurite growth (Moore et al., 2009). This suggests that in the adult nervous system, the presence of many growth-suppressive KLFs is dominant, and that

the developmental map of KLF expression in CNS neurons may induce specific axon growth phenotypes, though the specific network regulation between these factors is still unclear.

A number of KLF gene targets have been identified, mainly in studies outside the nervous system, but these may still be illuminating. Downstream gene targets of KLF7 in neurons include cyclin D1, p21, p27, L1, GAP-43, and genes important for synaptogenesis and cytoskeletal dynamics (Laub et al., 2001; Laub et al., 2005; Kajimura et al., 2007). KLF7 can also regulate the expression of TrkA, through binding to the TrkA enhancer together with the transcription factor Brn3a (Lei et al., 2006). Downstream gene targets of KLF9 include sodium, calcium, and potassium channels, which, as activity enhances trophic responsiveness and axon growth (Goldberg et al., 2002), could explain the decrease in dendrite arborization in Purkinje cells (Morita et al., 2003; Scobie et al., 2009). Whereas gene targets for KLF5 have not been described in the nervous system, in other systems, KLF5 has been shown to activate transcription of integrin-linked kinase (ILK) , as well as its targets Cdc42 and myosin light chain (Yang et al., 2008). A number of KLF4 targets identified outside of the nervous system may be good candidates for mediating KLF4's effect on axon growth, such as $p21^{WAF1/Cip1}$ (p21), p53, urokinase plasminogen activator receptor (u-PAR), ornithine decarboxylase (ODC), and three different laminin chains (Rowland and Peeper, 2006). Removal of KLF4's DNA-binding domain eliminated its ability to modulate neurite growth in vitro, suggesting a need for its transcriptional activity for the phenotypic change in neurite growth (Moore et al., 2009). It is presently unknown whether KLFs regulate the expression of these genes in neurons, or whether these or other target genes mediate the effect of KLFs on CNS axon growth. Nevertheless, a variety of gene targets of KLFs outside the nervous system may be excellent candidates to mediate their effects on neurite growth within the nervous system.

CONCLUSIONS

Transcription Factor Cross-Regulation of Axon Growth

The transcription factors p53, c-Jun, ATF3, CREB, STAT3, NFATs, NFkB, Sox11, SnoN, and the KLF family have been shown to affect neurite growth and axon regeneration. The way they do so is varied, but there are patterns that are revealed when we look at the studies as a whole. First, their developmental regulation is consistent with developmental axon growth patterns—pro-axon growth transcription factors are often more highly expressed early in development when axons are normally growing to their targets. Second, pro-axon growth transcription factors are often upregulated in regenerating neurons but not in neurons that fail to regenerate. Third, when both growth suppressive and growth enhancing transcription factors are expressed, the growth suppressors may dominate (Moore et al., 2009). Thus to optimally promote axon growth, it may be necessary to simultaneous turn off some and turn on other transcription factors.

As discussed above, these families of transcription factors often interact in regulating axon growth and regeneration. A significant component of this regulation is mediated through additional layers of complexity that are only partially understood. Transcription factors can function differently in different cell types due to the specific expression profile of co-factors in a given cell. The pairings of homodimers or heterodimers within transcription factor families or between superfamilies also increases this intricacy. They are able to compete for binding sites, making the relative expression levels of the factors in a specific cell important for their functional outcome, whether acting redundantly or in opposition. Finally, post-translational modifications of the transcription factors themselves may greatly affect gene regulatory outcomes. We have reviewed examples of these above, and for the KLFs in a recent publication (Moore et al., 2011). Because of the specific gene targets, and the

expression profile of different modulating factors or co-factors in different neurons, there is an inherent need for research on transcriptional control of gene targets potentially relevant for axon growth and regeneration to be performed in neurons, to better understand the transcription factors' cell-type specific role. This complexity, while seeming incredibly daunting, also likely provides the specificity and fine tuning needed for these transcription factors to regulate such intricate processes as regeneration, and a better understanding of these regulatory networks may lead to new approaches to understanding neural development and enhancing axon regeneration.

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