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INVITED REVIEW

Molecular mechanisms of the suppression of axon regeneration by KLF transcription factors

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Abstract

Molecular mechanisms of the Krüppel-like family of transcription factors (KLFs) have been studied more in proliferating cells than in post-mitotic cells such as neurons. We recently found that KLFs regulate intrinsic axon growth ability in central nervous system (CNS) neurons including retinal ganglion cells, and hippocampal and cortical neurons. With at least 15 of 17 KLF family members expressed in neurons and at least 5 structurally unique subfamilies, it is important to determine how this complex family functions in neurons to regulate the intricate genetic programs of axon growth and regeneration. By characterizing the molecular mechanisms of the KLF family in the nervous system, including binding partners and gene targets, and comparing them to defined mechanisms defined outside the nervous system, we may better understand how KLFs regulate neurite growth and axon regeneration.

Key Words: *optic nerve; regeneration; axon growth; retina; retinal ganglion cells; spinal cord; transcription factors*

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Introduction

Why do neurons in the central nervous system (CNS) fail to regenerate their axons after injury? This fundamental question has obvious implications for human neurodegenerative disease and injury (Moore and Goldberg, 2010). In the CNS, embryonic or neonatal neurons can regenerate their axons after injury, whereas postnatal or adult neurons cannot (Bregman and Goldberger, 1982; Kunkel-Bagden et al., 1992). This is at least partially attributable to the development of an inhibitory CNS environment, in which glial cells such as mature astrocytes and oligodendrocytes express molecules that suppress axon regeneration for example after injury in the adult mammalian CNS (Waxman, 1980; Foran and Peterson, 1992). After injury, damaged axons are exposed to myelin- and astrocyte-associated lipids and proteins that actively inhibit axon growth and regeneration (Yiu and He, 2006). For example, astrocytes secrete chondroitin sulfate proteoglycans (CSPGs) (Snow et al., 1990; McKeon et al., 1999; Becker and Becker, 2002; Jones et al., 2002, 2003; Tang et al., 2003) and oligodendrocytes express myelin-derived axon growth inhibitors including Nogo, myelin associated glycoprotein (MAG), and oligodendrocyte myelin glycoprotein (OMgp). When such molecules are genetically knocked out (Bartsch et al., 1995; Kim et al., 2003; Simonen et al., 2003; Zheng et al., 2003; Su et al., 2008), neutralized through antibody treatments (Caroni and Schwab, 1988; Bregman et al., 1995; Tang et al., 2001), or enzymatically digested (Crespo et al., 2007) in animal models, modest regeneration and improvement in behavioral assays is observed in animal models (Schmandke et al., 2007). Incomplete regeneration in all of these studies suggested the existence of other pathways involved in regenerative failure and motivated the search for signaling pathways intrinsic to the neurons themselves that may limit their regenerative ability.

Intrinsic control of axon regenerative ability and KLFs

A number of signaling molecules have been identified to act in neurons to limit regenerative ability. Some of these are trivial extensions of the extrinsic, inhibitory environment, such as receptors for inhibitory glial-associated proteins (Cafferty and Strittmatter, 2006) or signaling proteins downstream of these, such as rho and rho kinases (Bertrand et al., 2007). Others are signaling pathways involved more generally in cell growth regulation, such as anaphase promoting complex (APC) (Konishi et al., 2004; Lasorella et al., 2006), and phosphatase and tensin homolog (PTEN; (Park et al., 2008)) or neurotrophic factor responsiveness such as suppressor of cytokine signaling-3 (SOCS3; (Smith et al., 2009)),

cyclic adenosine 3′,5′-monophosphate (cAMP; (Cai et al., 2001)), and cAMP response element-binding protein (CREB; (Gao et al., 2004)).

Over the past few decades, multiple studies have demonstrated a developmental decrease in the intrinsic ability of CNS axons to rapidly elongate their axons (Saunders et al., 1992; Treherne et al., 1992; Li et al., 1995; MacLaren and Taylor, 1995; Saunders et al., 1995; Chen et al., 1997; Dusart et al., 1997; Blackmore and Letourneau, 2006), which correlates with the developmental loss of regenerative capacity *in vivo*. For example, embryonic retinal ganglion cells (RGCs) grow their axons ten-fold faster than postnatal RGCs, and this rapid axon growth ability is lost around the time of birth (Goldberg et al., 2002).

What is the molecular basis for this loss? When we analyzed microarray-derived transcriptomes from different ages of RGCs to identify developmentally regulated genes (Wang et al., 2007), we discovered that expression of the transcription factor Krüppel-like factor 4 (KLF4) significantly decreased neurite outgrowth in hippocampal and cortical neurons, and RGCs (Moore et al., 2009). Furthermore, KLF4 knockout during early development increased neurite growth from RGCs *in vitro*, and increased axon regeneration *in vivo* after optic nerve injury (Moore et al., 2009). Interestingly, KLF4 expression increases postnatally in RGCs, specifically during the period around birth, which is when RGCs lose their intrinsic axon growth ability (Moore et al., 2009). Moreover, another KLF family member, KLF9, also demonstrated a dramatic 250-fold increase in expression after birth. Overexpression of KLF9 was also shown to result in a significant decrease in neurite outgrowth *in vitro* (Moore et al., 2009). In general, these data support a model whereby the increase in KLF expression around birth, long after all RGCs have become post-mitotic, leads to a loss of regenerative ability of RGCs. Given KLF9's higher expression levels after birth relative to KLF4, and because it was closely related to subfamily members KLF13 and KLF16 that also suppressed axon growth, KLF9 became an intriguing target for studying molecular mechanisms governing its activity in RGCs, but little was known about its regulation or gene targets. We have recently found that knocking down expression of KLF9 with shRNA constructs strongly promotes RGC axon regeneration after optic nerve injury (unpublished data), and can help to identify both PTMs and downstream target genes required for KLF9 to suppress axon growth *in vitro* and regeneration *in vivo*.

Protein-protein interactions are an important regulatory mechanism of transcription factors within the CNS

Many proteins have been shown to interact with and regulate transcription factors in the CNS. Participation in these interactions often involves post-translational modifications (PTMs) of transcription factors such as acetylation, phosphorylation, ubiquitination, and sumoylation (Savare et al., 2005; Ceballos-Chavez et al., 2012; Goldberg and Trakhtenberg, 2012; Brochier et al., 2013). Such PTMs are critical in functional outcomes such as neuronal differentiation, survival and neurite growth (Cai et al., 2001; Hirata et al., 2003; Savare et al., 2005; Raivich and Makwana, 2007; Lai and Johnson, 2008; Raivich, 2008; Juliandi et al., 2010; Ceballos-Chavez et al., 2012; Hasegawa et al., 2012; Seo et al., 2012; Xie et al., 2012; Brochier et al., 2013; Watkins et al., 2013; Welsbie et al., 2013). Within the KLF family, KLF11 has been shown to interact with both histone acetyl and methyltransferases and these interactions have proven to be crucial in its functional role in regulating the dopamine D2 receptor in dopaminergic neurons (Seo et al., 2012). KLF5 has been shown to be activated by p300 and suppressed by SET in its ability to bind DNA and transactivate downstream target genes (Miyamoto et al., 2003).

KLFs are regulated by phosphorylation

Phosphorylation is perhaps the best studied PTM of transcription factors, and numerous kinase families affect neurite growth and regeneration. The MAPKs (ERKs, JNKs, and p38) and DLK families have been well studied in this regard. MAPK activation upon neuronal injury leads to changes in gene expression patterns mediated by phosphorylated TFs such as c-jun, SOX11, ATF2, P311, and STAT3 (Raivich and Makwana, 2007). These changes have varied effects including induction of heat shock proteins (HSP25/27) which spur the repair of the actin microfilament network (Stokoe et al., 1992; Cohen, 1996), promotion of survival by mitochondrial cytochrome c interference preventing caspase activation (Benn et al., 2002; Hirata et al., 2003; Dodge et al., 2006), and induction of programmed cell death (PCD) upon NGF withdrawal *via* release of inflammatory cytokines such as IL-1 and TNF-α (Xia et al., 1995).

Within the KLF family, we have shown that a MAPK family member regulates KLF9 at two critical residues and that this regulation is crucial to its functional role as a neurite outgrowth suppressor in RGCs (unpublished data). This form of regulation *via* phosphorylation is not unique to KLF9 among the KLF family. KLF6 has been shown to be regulated by phosphorylation in COS-7 cell lines metabolically labeled with radioactive phosphate, where it acts as a tumor suppressor (Slavin et al., 2004), but the kinase responsible remains unidentified. Using protein kinase inhibitors, it was demonstrated that KLF5 is activated by phosphorylation in its role as an oncogene and interacts with protein kinase C (PKC) and p38 but not MAPK in both human pancreatic and breast cancer cell lines (Zhang and Teng, 2003; Mori et al., 2009). KLF11 has been shown to be phosphorylated in 2 linker regions by ERK in CHO cell lines using in vitro phosphorylation assays (Ellenrieder et al., 2002; Ellenrieder, 2008). KLF4 is phosphorylated by PKC at T401, an important regulatory residue, in vascular smooth muscle cell differentiation *via* SMADs in a TGF-β and p38 dependent cascade (Zhang et al., 2012). KLF9, however, is thus far unique both in its capacity to bind the MAPK family of kinases and known to be regulated by them within neurons. Besides KLF9, only KLF10 and -11 possess the same structural motif necessary for KLF9-MAPK interaction. This might place these KLFs in signaling modules dependent on these specific kinases. The involvement of these kinases in the regulation

of KLFs outside the CNS makes them potential players in the intrinsic control of neurite growth both during normal neuronal development and after injury within the CNS. Characterizing the phosphorylation and phospho-regulation of other KLF family members within the CNS is thus an important goal for future study.

Conclusions

The finding that kinases such as those in the MAPK family, which are activated by extracellular signals such as neurotrophic factors or other signaling ligands, act on developmentally regulated transcription factors such as KLFs, has important implications for understanding regenerative failure. Such interactions may link the extrinsic regulators of axon growth including growth promoters and growth inhibitors to intrinsic, cell-autonomous signaling pathways. Understanding these networks may yield better approaches for promoting CNS axon regeneration.

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Author contributions: *Apora A and Goldberg JL wrote the paper. Both of these two authors approved the final version of this manuscript.*
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