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Review

Krüppel-like transcription factors in the nervous system: Novel players in neurite outgrowth and axon regeneration

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ABSTRACT

The Krüppel-like family of transcription factors (KLFs) have been widely studied in proliferating cells, though very little is known about their role in post-mitotic cells, such as neurons. We have recently found that the KLFs play a role in regulating intrinsic axon growth ability in retinal ganglion cells (RGCs), a type of central nervous system (CNS) neuron. Previous KLF studies in other cell types suggest that there may be cell-type specific KLF expression patterns, and that their relative expression allows them to compete for binding sites, or to act redundantly to compensate for another's function. With at least 15 of 17 KLF family members expressed in neurons, it will be important for us to determine how this complex family functions to regulate the intricate gene programs of axon growth and regeneration. By further characterizing the mechanisms of the KLF family in the nervous system, we may better understand how they regulate neurite growth and axon regeneration.

Contents

Abbreviations: CNS, central nervous system; RGC, retinal ganglion cell; KLF, Krüppel-like factor; E, embryonic; P, postnatal; cAMP, cyclic adenosine 3′,5′-monophosphate; CREB, cAMP response element-binding protein; Bcl-2, B-cell lymphoma/leukemia; Cdh1-APC, anaphase promoting complex; PTEN, phosphatase and tensin homology; CBP, CREB-binding protein; HDAC3, histone deacetylase 3; CtBP1, C-terminal-binding protein 1; NMDA, N-methyl-D-aspartic acid; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate; u-PAR, urokinase plasminogen activator receptor; ODC, ornithine decarboxylase; ATF3, activating transcription factor 3; SPRR1a, small proline rich protein 1a; MMP, matrix metalloproteinases; Arg I, Arginase I; Sp, specificity protein; BTD, Buttonhead; PNS, peripheral nervous system; GAP-43, growth-associated protein 43; TrkA, neurotrophic tyrosine kinase, receptor, type 1; TrkB, tropomyosin-related kinase B; T3, thyroid hormone; T3RE, T3 response element; AChE, acetylcholinesterase; DG, dentate granule; BTEB, basic transcription element binding protein; ILF, integrin-linked kinase; Cdc42, cell division control protein 42; AP-2α, activating enhancer-binding protein 2α; ChIP, chromatin immunoprecipitation; ATF3, activating transcription factor 3; STAT3, signal transducer and activator of transcription 3; NFAT, nuclear factor of activated T-cells; NFκB, nuclear Factor-KappaB; Sox11, SRY-box containing gene 11.

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Introduction

Why do neurons in the central nervous system (CNS) fail to regenerate their axons after injury? This has remained a fundamental question in neuroscience, with obvious implications for human disease (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 has been partially attributed to the development of an inhibitory CNS environment. Both mature astrocytes and mature oligodendrocytes contribute to an inhibitory environment for axon regeneration in the injured adult mammalian CNS. Between the first and second postnatal week of development in most CNS tissues, oligodendrocytes begin to form myelin sheaths around axons to allow for increased conduction of electrical impulses (Foran and Peterson, 1992; Waxman, 1980). After injury, damaged axons are exposed to the myelin-associated lipids and proteins that are inhibitory to axon growth and regeneration (reviewed in Yiu and He, 2006). Astrocytes respond to injury by secreting chondroitin sulfate proteoglycans (CSPGs) which are also inhibitory to growth (Becker and Becker, 2002; Jones et al., 2003, 2002; McKeon et al., 1999; Snow et al., 1990; Tang et al., 2003). Many strategies have been attempted to overcome glial-associated inhibitory cues and thus increase CNS regeneration. For example, many inhibitory proteins such as the myelin-derived axon growth inhibitor "Nogo", myelin associated glycoprotein "MAG", and oligodendrocyte myelin glycoprotein (OMgp) have been knocked out at the genetic level (Bartsch et al., 1995; Kim et al., 2003; Simonen et al., 2003; Su et al., 2008; Zheng et al., 2003), neutralized through antibody treatments (Bregman et al., 1995; Caroni and Schwab, 1988; Tang et al., 2001), or enzymatically digested (reviewed in Crespo et al., 2007). These studies have resulted in modest regeneration, leading to alternative strategies targeting the downstream signaling of these inhibitory pathways (reviewed in Schmandke and Strittmatter, 2007). The incomplete regeneration in all of these studies suggests that there may be additional inhibitory proteins that have yet to be discovered still acting to inhibit growth, and that there may be intrinsic changes within the neurons themselves that limit their regenerative ability.

An involvement of KLFs in the intrinsic control of axon regenerative ability

It has long been known that there is a developmental decrease in the ability of CNS axons to grow in vitro or regenerate in vivo (Blackmore and Letourneau, 2006; Chen et al., 1995; Dusart et al., 1997; Li et al., 1995; MacLaren and Taylor, 1995; Saunders et al., 1992, 1995; Treherne et al., 1992). For example, in spinal cord injury experiments in whole CNS preparations from neonatal opossums and embryonic rat, the injured neonatal CNS can regenerate, and this ability is lost postnatally (MacLaren and Taylor, 1995; Saunders et al., 1992, 1995; Treherne et al., 1992). In purified in vitro cultures, where RGCs are removed from all other contaminating cell types, embryonic RGCs grow their axons ten-fold faster than postnatal RGCs, with this growth ability lost specifically around the time of birth (Goldberg et al., 2002b). These data suggest that CNS neurons lose their intrinsic capacity for rapid axon growth during development, and that this may play a role in the regenerative failure of CNS axons after injury.

What is the molecular basis for this loss? Prior work has pointed to possible roles for cyclic adenosine 3′,5′-monophosphate (cAMP; Cai et al., 2001), cAMP response element-binding protein (CREB; Gao et al., 2004), B-cell lymphoma/leukemia (Bcl-2; Chen et al., 1997; Cho et al., 2005), anaphase promoting complex (APC) signaling pathways (Konishi et al., 2004; Lasorella et al., 2006) and phosphatase and tensin homology (PTEN; Park et al., 2008) in this loss (Box 1). To identify new candidate genes that could contribute, we analyzed microarray-derived transcriptomes from different ages of RGCs to reveal developmentally regulated genes (Wang et al., 2007). These genes were screened in primary neurons for their effect on neurite outgrowth.

Overexpression of the transcription factor Krüppel-like factor 4 (KLF4) resulted in a significant decrease in neurite outgrowth in hippocampal and cortical neurons, and RGCs (Moore et al., 2009). KLF4 knockout during early development resulted in increased neurite growth from RGCs in vitro, and increased axon regeneration in vivo after optic nerve injury which was unrelated to RGC differentiation (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). These data support a model whereby the increase in KLF4 expression around birth, long after all RGCs have become post-mitotic, leads to a loss of regenerative ability of RGCs (Moore et al., 2009).

Box 1
Some of the intracellular signaling molecules with roles in CNS regeneration.

cAMP. Endogenous cAMP levels influence the developmental loss of regenerative capacity in retinal ganglion cells (Cai et al., 2001).

CREB. Downstream of cAMP, the activated transcription factor CREB is essential for spinal neurons to overcome the inhibitory injury environment (Gao et al., 2004).

Bcl-2. The proto-oncogene bcl-2 enhances retinal axon regeneration in certain assays (Chen et al., 1997).

Cdh1-APC. These and other cell cycle regulators also negatively influence axon growth in cerebellar granule neurons (Konishi et al., 2004).

PTEN. Deletion of this negative regulator of the mammalian mTOR pathway significantly promotes axon regeneration in retinal ganglion cells in vivo (Park et al., 2008).

KLFs. Krüppel-like factors regulate, positively and negatively, axon growth of CNS neurons in vitro and in vivo (Moore et al., 2009).