A gene network perspective on axonal regeneration

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The regenerative capacity of injured neurons in the central nervous system is limited due to the absence of a robust neuron-intrinsic injury-induced gene response that supports axon regeneration. In peripheral neurons axotomy induces a large cohort of regeneration-associated genes (RAGs). The forced expression of some of these RAGs in injured neurons has some beneficial effect on axon regeneration, but the reported effects are rather small. Transcription factors (TFs) provide a promising class of RAGs. TFs are hubs in the regeneration-associated gene network, and potentially control the coordinate expression of many RAGs simultaneously. Here we discuss the use of combined experimental and computational methods to identify novel regeneration-associated TFs with a key role in initiating and maintaining the RAG-response in injured neurons. We propose that a relatively small number of hub TFs with multiple functional connections in the RAG network might provide attractive new targets for gene-based and/or pharmacological approaches to promote axon regeneration in the central nervous system.

Keywords: axon regeneration, sciatic nerve injury, gene regulatory network, gene therapy

REGENERATION-ASSOCIATED GENES: A HISTORICAL PERSPECTIVE

The extent to which neurons can regenerate injured axons varies dramatically in the adult mammalian nervous system. Axotomy of peripheral neurons results in the activation of hundreds of neuron-intrinsic regeneration-associated genes (RAGs), whereas in many central neurons a very limited or no RAG-response is observed, except following very proximal lesions (Jenkins et al., 1993; Fernandes et al., 1999; Mason et al., 2003). In addition to the inhibitory extracellular environment of the CNS, the absence of a coordinated RAG-response is a major reason for regenerative failure in the CNS. Early findings that particular axonal proteins, such as GAP-43 and alpha-tubulin, are induced in injured peripheral neurons led to the hypothesis that peripheral nerve injury triggers an intrinsic cell body response that includes the expression of a set of growth-associated proteins (GAPs) that together promote axon regeneration (Skene and Willard, 1981; Skene, 1989; Tetzlaff et al., 1991).

The idea that successful regeneration of injured axons also requires an appropriate intrinsic RAG-response is further supported by several other observations. Firstly, although CNS neurons do not regenerate spontaneously, if a peripheral nerve graft is implanted into the spinal cord, some spinal neurons (on average 100–200 per animal), actually can regenerate injured axons into the graft (David and Aguayo, 1981; Richardson et al., 1982), indicating that certain central neurons do have the intrinsic capacity to regenerate injured axons when provided with a suitable growth-stimulating environment. CNS neurons that are able to regenerate into nerve grafts also upregulate RAGs following axotomy (Anderson et al., 1998; Mason et al., 2002). It is important to note, however, that most injured neurons in the spinal cord do not show such a response, and that the majority of neurons that do are located very close to the lesion site. Secondly, treatment of rubrospinal neurons with BDNF at their cell bodies results in upregulation of GAP expression and promotes regeneration of axons into peripheral nerve transplants in the spinal cord (Kobayashi et al., 1997), even when neurons are chronically lesioned and severely atrophied (Kwon et al., 2002). Thus, exogenous treatments that boost RAG expression in these neurons also increase the number of regeneration-competent cells. Thirdly, when dorsal root ganglion (DRG) neurons are conditioned by a peripheral nerve transaction, a lesion which induces RAG expression, their central axons show an enhanced regenerative response that can result in significant sprouting into the spinal cord, even beyond the lesion site (Richardson and Issa, 1984; Chong et al., 1999; Neumann and Woolf, 1999). Finally, this conditioning lesion effect was shown to be transcription dependent (Smith and Skene, 1997). Together these findings all indicate that a coordinated neuron-intrinsic regeneration-associated transcriptional response is critical for successful axonal regeneration to occur, and are in support of the RAG-hypothesis.

By now, genome-wide gene expression profiling studies have provided a near-complete view of the complex changes in neuronal gene expression in diverse PNS and CNS injury paradigms
(Costigan et al., 2002; Xiao et al., 2002; Schmitt et al., 2003; Kury et al., 2004; Di Giovanni et al., 2005; Bosse et al., 2006; Stam et al., 2007; Geeven et al., 2011). Meta-analyses of these transcriptional profiling studies revealed the core set of RAGs that is consistently upregulated following neuronal injury (Szpara et al., 2007; Stam et al., 2008). These studies have further supported the original RAG-hypothesis by showing that many genes are strongly upregulated during successful regeneration, whereas types of injury (e.g., dorsal root injury) that are not followed by successful regeneration, do not robustly induce their expression.

The identification of RAGs led to the idea that axon regeneration could be promoted by manipulating the expression of specific RAGs in injured neurons. Initial studies using transgenic GAP-43 mice were promising and showed an enhancement of long-distance regenerative axon growth in the PNS (Aigner et al., 1995). In the CNS, however, overexpression of GAP-43 only induced nerve sprouting, but failed to induce long-distance regeneration (Aigner et al., 1995; Buffo et al., 1997; Neumann and Woolf, 1999), even into growth-permissive peripheral nerve grafts (Mason et al., 2000). Also, GAP-43 knockout mice have no gross axonal growth deficits, but show profound defects in axonal guidance (Strittmatter et al., 1995; Sretavan and Kruger, 1998; Maier et al., 1999; Zhu and Julien, 1999). Other classical RAGs that have only limited effects on axon regeneration include Spry1a and Igga7 (Werner et al., 2000; Bonilla et al., 2002; Raivich et al., 2004). These findings demonstrate that manipulating the expression of individual RAGs does not induce robust axon regeneration in the CNS, and therefore research started to focus on transcriptional regulators that can affect the expression of multiple RAGs jointly.

THE RAG REGULATORY NETWORK: REGENERATION-ASSOCIATED TRANSCRIPTION FACTORS

All cellular processes are controlled by genes that act together in regulatory networks. Gene regulatory networks are inherently robust against random perturbation (Albert et al., 2000), which may explain why manipulating the expression of individual RAGs has a limited effect on axon regeneration. One way to alter the state of the network is to jointly manipulate the expression of multiple genes in the network. Indeed, overexpression of both Gap-43 and Gap23 in the RAG network resulted in enhanced DRG regeneration into peripheral nerve grafts implanted in the spinal cord (Bomze et al., 2001). There are however practical limitations to the number of RAGs that can be simultaneously overexpressed. As an alternative, one could change the expression of so-called hub genes in the RAG network. Hub genes are highly connected nodes in a gene network and regulate the coordinated expression or activity of many other genes. They are therefore attractive candidate targets for perturbation at the network level (Batada et al., 2006; Figure 1).

Hubs in gene regulatory networks are often transcription factors (TFs). C-JUN was the first TF to be identified in the RAG network (Herdegen et al., 1991; Jenkins and Hunt, 1991), and plays an important role in the successful regeneration of facial nerve motor neurons (Raivich et al., 2004). Later, additional regeneration-associated TFs were identified, including ATF3, SOX11, CREB, p53, STAT3, KLF4, and SMAD1 (Schwaiger et al., 2000; Tsujino et al., 2000; Gao et al., 2004; Di Giovanni et al., 2006; Jankowski et al., 2006; Seijffers et al., 2006; Moore et al., 2009; Zou et al., 2009). Some of these TFs are now recognized as important regulators of specific subsets of RAGs. For instance, C-JUN induces expression of Igga7 (with Iggb1 the receptor for laminin), the cell adhesion molecule Cad44, and the neuropeptide Gal (Raivich et al., 2004), and ATF3 induces expression of c-Jun, the heat-shock protein.
We were intrigued by the fact that NFIL3 is upregulated in DRG sensory neurons by peripheral nerve injury (Stam et al., 2007), but that suppressing NFIL3 expression strongly enhances axon growth of cultured adult DRG neurons (Macgillavry et al., 2009). The relation between the injury-induced expression of a TF and its apparent role in regeneration can indeed be quite paradoxical, and at least three other studies have shown examples of RAGs that repress axon growth. SOCS3, for instance, is induced in DRG neurons by a peripheral nerve lesion, but represses axon growth by inhibiting the growth-promoting TF STAT3 (Miao et al., 2006). The regeneration-promoting effects of cAMP on injured retinal ganglion cells appear to be mediated by a downregulation of SOCS3 (Park et al., 2009). Genetic deletion of SOCS3 promotes optic nerve regeneration (Smith et al., 2009), whereas overexpression of SOCS3 inhibits optic nerve regeneration (Hellstrom et al., 2011). Another study demonstrated that NFAT-3 is a transcriptional repressor of Gap-43 expression (Nguyen et al., 2009). This was unexpected, as it is long known that NFATs are activated in response to growth factors and mediate axon growth and pre-synaptic differentiation (Graef et al., 2003). Finally, KLF4 was identified as a repressor of axon growth (Moore et al., 2009; Blackmore et al., 2010). Although KLF4 expression is not upregulated after injury (Szpara et al., 2007; Stam et al., 2008), in vivo deletion of KLF4 does enhance optic nerve regeneration (Moore et al., 2009). Moreover, the same study showed that several other KLF family members also suppress axon growth, while two others, KLF6 and KLF7, promote axon growth.
In an attempt to understand the role of NFIL3 in the RAG regulatory network, we further studied how NFIL3 regulates RAG expression. We showed that NFIL3 expression follows cAMP induction and CREB activation, and that NFIL3 suppresses CREB target genes such as Arg1 and Gap-43, by competing for the same DNA binding sites (Macgillavry et al., 2009; Figure 2). Such so-called incoherent feed-forward loops occur in many other gene regulatory networks, and allow efficient control of target gene dynamics (Kaplan et al., 2008). CREB and NFIL3 are widely expressed in the brain, and their feed-forward interactions may have evolved to create strict temporal control over the expression of elasticity genes. In a subsequent study, we identified C/EBP TFs as part of this regulatory loop. CREB induces C/EBP expression in neurons, and NFIL3 also suppresses many C/EBP target genes (Macgillavry et al., 2011; Figure 2). Together, these findings for the first time reveal a part of the gene regulatory network architecture underlying neuronal regeneration, and suggest that genetic mechanisms to fine-tune neuronal plasticity form an evolutionary constraint on a neuron’s ability to regenerate injured axons.

RAG NETWORK HUBS: THERAPEUTIC PERSPECTIVE

Insights into RAG network architecture, and the identification of hub TFs within the network, may aid the future development of gene therapeutic and pharmacological strategies to enhance the intrinsic regenerative potential of injured central neurons. Although direct translation of current knowledge into clinically relevant therapeutic approaches is not possible yet, we are tempted to make some predictions. NFIL3, for instance, is widely expressed in the CNS, and may serve to suppress or fine-tune CREB-dependent plasticity. If NFIL3 indeed also represses regenerative axon growth in the CNS, then our findings would predict that a transient relief of NFIL3-mediated repression might temporarily enhance the effects of CREB and stimulate axonal regeneration. Gene therapy is an ideal method to deliver or inactivate hub TFs, as it can selectively target the desired neurons and allows simultaneous overexpression of growth-promoting TFs and suppression of growth-inhibiting TFs, at least for pre-clinical studies. We, and others, have explored the use of vectors based on lentivirus and adeno-associated virus (AAV) for gene delivery to the nervous system. AAV vectors are highly effective for gene delivery to DRG neurons and rubrospinal neurons (Hollis et al., 2008; Blits et al., 2010; Mason et al., 2010; Parikh et al., 2011; Figure 3). AAV vectors are also promising as vectors that can be delivered via the CSF intrathecally (Storek et al., 2008; Towne et al., 2009), although such an untargeted delivery method may be unsuitable when the intervention is required only in specific neuronal populations.

A major challenge is how to regulate gene expression so that it can be turned off when no longer required, whether this is days or months after application of the vector (Mason et al., 2011), as a continued growth response may eventually have undesirable consequences. Other developments will include the methods to deliver multiple transgenes simultaneously to the same neuron, for example using AAV vectors with multiple promoters. AAV vectors in particular, hold great promise as clinically acceptable gene therapy vectors for the promotion of CNS regeneration since they have proven to be well-tolerated and safe in patients.

CONCLUDING REMARKS

Hub TFs in the RAG regulatory network provide an attractive class of molecular targets for promoting the regenerative capacity of injured neurons because they jointly regulate the expression of many RAGs simultaneously. Interestingly, recent studies into RAG network architecture showed that some regeneration-associated TFs actually suppress the regenerative capacity of neurons. Such intrinsic inhibitors of neuronal regeneration may provide interesting targets to inactivate using viral vector approaches. Ideally, the combined expression and/or inactivation of a few hub TFs in the RAG network will be sufficient to enhance the regeneration of axotomized central neurons, and we expect that further elucidation of RAG network architecture will aid the selection of therapeutically relevant TF targets in the future.
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