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<th>Targeting transcriptional regulators to regenerate midbrain dopaminergic axons in Parkinson’s disease</th>
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<td>Authors</td>
<td>Hegarty, Shane V.; Sullivan, Aideen M.; O’Keeffe, Gerard W.</td>
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<tr>
<td>Publication date</td>
<td>2017</td>
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<tr>
<td>Type of publication</td>
<td>Article (peer-reviewed)</td>
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<tr>
<td>Link to publisher’s version</td>
<td><a href="http://www.nrronline.org/article.asp?issn=1673-5374;year=2017;volume=12;issue=11;spage=1814;epage=1815;aulast=Hegarty">http://www.nrronline.org/article.asp?issn=1673-5374;year=2017;volume=12;issue=11;spage=1814;epage=1815;aulast=Hegarty</a> - 10.4103/1673-5374.219039</td>
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<td>Download date</td>
<td>2024-05-08 07:06:09</td>
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<td>Item downloaded from</td>
<td><a href="https://hdl.handle.net/10468/5380">https://hdl.handle.net/10468/5380</a></td>
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Targeting transcriptional regulators to regenerate midbrain dopaminergic axons in Parkinson’s disease

Introduction: Parkinson’s disease (PD) is a chronic, age-related neurodegenerative disorder that affects 1–2% of the population over the age of 65. PD is characterised by the progressive degeneration of nigrostriatal dopaminergic (DA) neurons. This leads to disabling motor symptoms, due to the striatal DA denervation. Despite decades of research, there is still no therapy that can slow, stop or regenerate the dying midbrain DA neurons in PD. Current drug treatment regimes typically involve dopamine-replacement strategies. While these are effective in controlling the symptoms for several years, they do not attenuate the progressive neurodegeneration. There is now robust evidence that retrograde degeneration of nigrostriatal axons occurs early in PD pathogenesis, and precedes neuronal loss (Kordower et al., 2013). Therefore, a promising approach for restoring motor function in PD patients may be to develop strategies which regenerate nigrostriatal DA axons, so that they can re-establish their lost connections (Figure 1). To address this, investigation of the potential for reactivation of the intrinsic axon growth capacity of midbrain DA neurons is needed. Information on the molecular mechanisms regulating nigrostriatal DA axonal growth and target innervation during their normal development will provide novel targets for axon regenerative therapy in PD.

Axon regeneration in the central nervous system (CNS): Regeneration of CNS axons remains a major challenge for contemporary neuroscience. While their peripheral nervous system (PNS) counterparts can typically regenerate after damage in adulthood, the spontaneous regeneration of injured CNS axons is inhibited by a number of extrinsic factors, such as glial barriers and myelin-associated inhibitors. Moreover, it is now well established that intrinsic growth ability is a critical determinant of CNS axon regeneration (He and Jin, 2016). In the case of the degenerating nigrostriatal pathway, axon regrowth is arrested by PTEN deletion, or knocking down Krüppel-like factor 4 (KLF4), as a transcriptional repressor of midbrain DA axon growth. Genetic manipulation of KLF4 in vivo, in a Smad signaling-dependent manner (Hegarty et al., 2015). In our study, we discovered that Zeb2 was first identified as a transcriptional repressor that interacts with Smad transcription factors, and has since been shown by many studies to be a multifunctional regulator of nervous system development (Hegarty et al., 2015). In our study, we discovered that Zeb2 acts as a repressor of midbrain DA axon growth. Genetic silencing of Zeb2 enhanced, while Zeb2 overexpression repressed, midbrain DA axonal growth in vitro, in a Smad signalling-dependent manner (Hegarty et al., 2017). Moreover, we demonstrated that conditional (Nestin-Cre based) Zeb2 knockout mice exhibit DA hyperinnervation of the striatum, indicating that nigrostriatal DA axons grow excessively in the absence of Zeb2 in vivo.

Molecular regulation of midbrain DA axonal growth: To identify such regulators of midbrain DA axon growth, we recently performed a polymerase chain reaction (PCR) screen to profile gene expression in the mouse midbrain during nigrostriatal pathway development (Hegarty et al., 2017). We found that expression of zinc finger E-box-binding homeobox 2 (Zeb2) was significantly decreased during nigrostriatal pathway development (Hegarty et al., 2017). We found that expression of zinc finger E-box-binding homeobox 2 (Zeb2) was significantly decreased during nigrostriatal pathway development (Hegarty et al., 2017). We found that expression of zinc finger E-box-binding homeobox 2 (Zeb2) was significantly decreased during nigrostriatal pathway development (Hegarty et al., 2017). We found that expression of zinc finger E-box-binding homeobox 2 (Zeb2) was significantly decreased during nigrostriatal pathway development (Hegarty et al., 2017). We found that expression of zinc finger E-box-binding homeobox 2 (Zeb2) was significantly decreased during nigrostriatal pathway development (Hegarty et al., 2017). We found that expression of zinc finger E-box-binding homeobox 2 (Zeb2) was significantly decreased during nigrostriatal pathway development (Hegarty et al., 2017).
mechanistic findings obtained from the widely-used optic nerve crush model are comparable or predicative for other CNS axonal projections, then Zeb2 may be a promising target for the regeneration of nigrostriatal DA axons, since we have found that it represses midbrain DA axonal growth during development (Hegarty et al., 2017). In support of this suggestion, axon regeneration strategies developed from the optic nerve model have been used to regenerate corticospinal axons (Du et al., 2015; He and Jin, 2016). To explore the potential of Zeb2 as a therapeutic target in PD, the regenerative effects of Zeb2 knockdown on nigrostriatal DA axons should be investigated in animal models of PD. Furthermore, those regeneration-enhancing manipulations that relate to both RGC and corticospinal axons, and thus may be universally applicable throughout the CNS, e.g., PTEN deletion, should also be investigated for their ability to regenerate midbrain DA axons.

Potential limitations for regenerative therapy in PD: To date, experimental regeneration strategies have achieved successful regrowth of only a proportion of the population of injured or degenerating CNS axons (Park et al., 2008; Moore et al., 2009; Duan et al., 2015; He and Jin, 2016; Norsworthy et al., 2017). Further research is therefore required to overcome this limitation, such as the investigation of subtype-specific growth mechanisms in CNS neuronal populations. However, since nigrostriatal DA axons extensively innervate their target areas, axon regeneration of the total population of dying midbrain DA neurons may not be necessary to achieve clinical benefits in PD. For example, a neuronal labelling study showed that a single midbrain DA axon can innervate up to 5.7% of the total volume of the striatum (Matsuda et al., 2009). Therefore, it is theoretically possible to restore a therapeutically efficacious amount of striatal innervation in PD by inducing the regeneration of only a proportion of midbrain DA axons.

Another important consideration before regenerative therapy becomes a clinical possibility for PD is whether the nigrostriatal DA axons, which are subject to pathological, degenerative signals, will require both survival- and regeneration-promoting signals to effectively reinnervate the striatum. KLF4 deletion increases the regeneration of adult RGCs without affecting their survival (Moore et al., 2009), whereas Sox11 overexpression promotes regeneration of some RGC subtypes but kills others (Norsworthy et al., 2017). Because survival and regenerative signalling can be mutually exclusive, it will be important to test whether manipulations aimed at regenerating nigrostriatal DA axons, such as the proposed deletion of Zeb2, also have effects on neuronal survival in animal models of PD. For the effective, long-term restoration of nigrostriatal DA innervation in PD, regeneration therapeutics may need to be co-administered with survival-promoting treatments, e.g., neurotrophic factors. Other avenues that should be explored before translation from animal models to the clinic include: the quantification of the number of functional synapses established by regenerating axons, determination of any adverse effects of the genetic manipulation(s) on other key cellular functions, evaluation of the potential of task-specific training to enhance functional recovery after regenerative therapy, and optimisation of non-invasive methods for targeting regeneration enhancers in the CNS.

Despite these potential limitations, targeting transcriptional regulators, such as Zeb2, to regenerate midbrain DA axons is a promising disease-modifying therapeutic strategy for PD, and may be capable of achieving functional recovery for PD patients.

This study is supported by grants from the Irish Research Council (R15897; SVH/AMS/GWO’K) the National University of Ireland (R16189; SVH/AMS/GWO’K), Royal Irish Academy (SVH/AMS/GWO’K), and Science Foundation Ireland (15/CDA/3498; GWO’K).

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Accepted: 2017-11-11
doi: 10.4103/1673-5374.219039


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References


