REVIEW

Axon regeneration induced by environmental enrichment- epigenetic mechanisms

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Abstract

Environmental enrichment is known to be beneficial for cognitive improvement. In many animal models of neurological disorders and brain injury, EE has also demonstrated neuroprotective benefits in neurodegenerative diseases and in improving recovery after stroke or traumatic brain injury. The exact underlying mechanism for these phenomena has been unclear. Recent findings have now indicated that neuronal activity elicited by environmental enrichment induces Ca^{2+} influx in dorsal root ganglion neurons results in lasting enhancement of CREB-binding protein-mediated histone acetylation. This, in turn, increases the expression of pro-regeneration genes and promotes axonal regeneration. This mechanism associated with neuronal activity elicited by environmental enrichment-mediated pathway is one of several epigenetic mechanisms which modulate axon regeneration upon injury that has recently come to light. The other prominent mechanisms, albeit not yet directly associated with environmental enrichment, include DNA methylation/demethylation and N^6-methyladenosine modification of transcripts. In this brief review, I highlight recent work that has shed light on the epigenetic basis of environmental enrichment-based axon regeneration, and discuss the mechanism and pathways involved. I further speculate on the implications of the findings, in conjunction with the other epigenetic mechanisms, that could be harness to promote axon regeneration upon injury.

Key Words: *axon regeneration; CREB-binding protein; DNA methylation/demethylation; dorsal root ganglion; DRG neurons; environmental enrichment; epigenetics; histone acetylation; mechanistic target of rapamycin; mTOR; phosphatase and tensin homologue; PTEN*

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Introduction

Adult neurons, particularly those in the central nervous system (CNS), exhibit dismal levels of axon regeneration upon injury. Effective axon regeneration is blocked by both external inhibitory factors in the environment (Geoffroy and Zheng, 2014) and limited by neuronal intrinsic factors (He and Jin, 2016; Mahar and Cavalli, 2018), such as a robust response to injury with regards to new protein synthesis. In terms of cellular mechanisms that regulate axonal regeneration upon injury, a well-known signaling axis that underlie successful regeneration is that of the mechanistic target of rapamycin (mTOR) and phosphatase and tensin homologue (PTEN) (Park et al., 2010). mTOR activates the pro-survival phosphoinositide 3 kinase-AKT kinase pathway and enhances somatic and axonal protein synthesis, while PTEN antagonizes mTOR signaling. The latter is thus a key intrinsic inhibitor of axon regeneration, and PTEN deletion or silencing is invariably favorable for regeneration (Park et al., 2008; Christie et al., 2010; Liu et al., 2010; Zukor et al., 2013). It is well known that peripheral neurons are superior to CNS neurons in terms of axon regeneration, and a popular model to study intrinsic factors governing axon regeneration is the dorsal root ganglion (DRG) neurons (Nascimento et al., 2018). These pseudo-unipolar neurons have a stem axon with a peripheral and a central branch. Interestingly, the difficulty of axon regeneration by the central branch could be overcome by conditional injuries to the peripheral branch (Qiu et al., 2002), presumably via alteration of intrinsic regenerative capacity of the entire neuron.

Environmental enrichment (EE) is an experimental paradigm in which experimental animals are exposed to stimulatory physical and social surroundings. EE exposure has been shown, in general, to promote neuronal morphogenesis, synaptogenesis and increasing neuronal activity (Alwis and Rajan, 2014; Hannan, 2014). EE exposure has also been shown to be beneficial to a range of neurological disorder models. These include animal models of neurodegenerative diseases such as Alzheimer's disease (Verret et al., 2013; Griñán-Ferré et al., 2018), Parkinson's disease (Goldberg et al., 2012), amyotrophic lateral sclerosis (Stam et al., 2008) and Huntington's disease (Spires et al., 2004), neurodevelopmental disorders such as Rett Syndrome (Kondo et al., 2008), as well as those of traumatic (de la Tremblaye et al., 2019) or ischemic (Gonçalves et al., 2018) brain injuries.

The mechanism underlying the neuronal protective and beneficial effects of EE has not been particularly clear, but could involve the production of pro-regenerative neurotrophins or cytokines (Ickes et al., 2000; Rossi et al., 2006; Zhang et al., 2016). Interestingly, epigenetic mechanisms involving histone acetylation has been shown to underlie the increase in the pro-survival and regenerative neurotrophin brain-derived growth factor (BDNF) in the hippocampus of aged rats (Neidl et al., 2016). Furthermore, enhanced synaptic plasticity after EE in adult male mice could be transgenerationally inherited

via miRNAs (Benito et al., 2018). Pertaining to functional recovery after injury, EE-based factors likely act by promoting survival as well as the intrinsic regenerative capacity of adult neurons, including the capacity to regenerate severed or damaged axons. Recent findings made in DRG neurons have indeed implicate epigenetic changes in the form of enhanced histone acetylation in the damaged neuron as a major underlying driving processes for regeneration resulting from EE exposure. Here, I provide a short review of these findings, as well as other epigenetic mechanisms modulating axon regeneration that has come to light in the past 2–3 years. This narrative is informed by Medline database searches with the key word combinations of "environmental enrichment", "epigenetics" and "axon regeneration".

An Underlying Epigenetic Mechanism for Environmental Enrichment-Mediated Enhancement in Axon Regeneration of Proprioceptive Dorsal Root Ganglion Neurons

Hutson et al. (2019) have recently investigated the neuronal activity enhancement basis of EE on DRG neurons. The authors first observed that neurite outgrowth from DRG neurons from mouse placed in EE housing is significantly enhanced compared to those placed under standard housing. This enhancement was comparable to that induced by a conditioning injury, was gene transcription dependent, and was long lasting. Importantly, this enhancing effect of EE is larger than that induced by physical exercise alone. EE housing not only enhanced sciatic nerve axon regeneration, but also regeneration of sensory axons in a spinal cord injury (SCI) model, as traced by a retrograde marker. These regenerating sensory axons conferred a larger amplitude of compound action potentials recorded above the lesion site, which was selectively abolished by a chemo-genetics approach (using the Designer Receptors Exclusively Activated by Designer Drugs (DREADD) technology) targeting DRG neurons. The authors further noted that DRG neurons with axons regenerated across injury sites are positive for the proprioceptive neuron marker parvalbumin (PV), and that EE specifically enhanced neurite outgrowth from DRG neurons labeled by a PV promoter-driven fluorescent marker. Interestingly, EE-dependent (but not injury conditioning-dependent) DRG neurite outgrowth is largely abolished in *Egr3*$^{-/-}$ mice, which are defective in muscle spindle proprioceptive feedback but not PV-positive neuron population. These findings indicate that EE rather specifically enhances proprioceptive DRG axon regeneration, and that this enhancement is dependent on proprioceptive afferent feedback.

How did EE promote axonal regeneration? Interestingly, the authors observed no significant changes in either the DRG neurons or in the circulation in terms of neurotrophin and cytokine levels. RNAseq and proteomics analysis of whole DRGs (of mixed DRG neuronal cell types) or laser-captured DRG neurons with large diameter (which would include the proprioceptor and mechanoreceptor neuron populations) showed marked changes in the latter. In particular, EE induced an upregulation of genes and proteins associated with molecular pathways that are associated with regeneration, including those that regulate neuronal activity, calcium signaling, energy metabolism, neuronal projection and cytoskeleton dynamics. These changes in transcriptional and protein expression profiles are in line with the notion of an EE-induced pro-regenerative gene expression profile and activity in the DRG neuron subtypes examined. Indeed, Gi-coupled DREADD-mediated inhibition of adenylate cyclase and silencing of DRG neuronal activity attenuated axon regeneration of EE-exposed mice. Conversely, neuronal activity enhancement by Gq-coupled DREADD (which elicits inositol 1,4,5-trisphosphate-mediated Ca^{2+} release from intracellular stores) in mice on standard housing enhanced their DRG neurite outgrowth to a degree similar to those observed for the EE-exposed mice. Furthermore, the authors directly confirmed that EE exposure increases potassium stimulated Ca^{2+} release in the proprioceptive DRGs of transgenic mice carrying a calcium indicator GCaMP under the PV promoter (Hutson et al., 2019).

How did EE-induced neuronal activity elicit a global change in the proprioceptive DRG gene expression profile so as to enhance axon regeneration? The authors examined histone epigenetic marks and found that EE enhanced the acetylation of H3K27 and H4K8 in PV-positive DRG neurons. In line with the RNAseq finding of transcriptional upregulation, H4K8ac and H3K27ac are indeed markers of transcriptional activation. These histones could be acetylated by the CREB-binding protein (CBP), which harbors Ca^{2+}-sensitive transactivation domains and is known to play important roles in activity-dependent neuroplasticity. In this regard, CBP activity is known to be controlled by Ca^{2+} and the calcium/calmodulin-dependent (CaM) protein kinases II and IV (CaMKII/IV) (Chawla et al., 1998; Hu et al., 1999). CBP has also been previously shown to be necessary for EE-induced neurogenesis and cognitive enhancement (Lopez-Atalaya et al., 2011). Indeed, the current work shows that EE exposure increased CBP phosphorylation and acetylated (active) CBP levels in PV-positive DRG neurons. Levels of acetylated H4K8, like the enhancement of neurite outgrowth capacity, persisted in PV-positive DRG neurons for a long time, even 5 weeks after EE exposure. Both the levels of acetylated H4K8 and acetylated CBP were reciprocally enhanced or inhibited by the DREADD-mediated manipulations of neuronal activity, thus linking calcium-dependent neuronal activity to both CREB activation and histone acetylation. Importantly, in mice with CBP conditionally knocked out in Ca^{2+}-calmodulin-dependent protein kinase IIa (CaMKIIa)-positive neurons (including DRGs), loss of CBP abolished EE-exposure induced increase in neurite outgrowth. CBP-based acetylation is thus critical for mediating the persistent enhancement of neurite outgrowth and axon regeneration phenotype associated with neuronal activity resulting from EE exposure.

Could enhancement of CBP activity in the CNS therefore promote axon regeneration after injury? The authors demonstrated this point (Hutson et al., 2019) with a small molecule

activator of CBP (TTK21) conjugated to glucose-derived carbon nanospheres (CSP) (Chatterjee et al., 2013), with the latter allowing effective delivery across the blood-brain barrier. CSP-TTK21 increased neurite outgrowth of DRG neurons in culture and promoted axonal regeneration as well as sensorimotor function *in vivo* after mid-thoracic dorsal hemisection in a mouse SCI model. In another SCI model of mid-thoracic spinal cord contusion in rats, CSP-TTK21's enhancement of functional recovery appeared to correlate with the enhanced sprouting of both descending motor and ascending sensory axons, as well as an increase in the density of vGlut1-positive synaptic boutons from proprioceptive neurons found at the proximity of motor neurons. These findings, taken together, further supports the role of CBP activity in axon regeneration and attests to the translational value of this notion (**Figure 1**).

Epigenetics-Based Regulation of Axon Regeneration – Important Recent Findings

The findings of Hutson et al. (2019) illustrated an epigenetic mechanism underlying axon regeneration enhancement. In this regard, these findings add to other recent advances in our understanding of modulation of axon regeneration by several epigenetic mechanisms (Weng et al., 2016). There are major recent advances in our understanding of the role of DNA methylation in axon regeneration (Loh et al., 2017; Weng et al., 2017; Oh et al., 2018). Axotomy of mouse DRG neurons elevated the levels of the methylcytosine dioxygenase Ten-eleven translocation 3 (Tet3) (Loh et al., 2017; Weng et al., 2017). Tet3 mediates active DNA demethylation by catalyzing the conversion of 5-methylcytosine to 5-hydroxymethylcytosine and iteratively oxidizing it to 5-formylcytosine and 5-carboxycytosine. Genome-wide 5-hydroxymethylcytosine mapping showed that injury leads to distinct changes associated with regeneration-associated genes (RAGs), including the well-known ones such as *Atf3*, *Bdnf*, and *Smad1* (Loh et al., 2017). Tet3 silencing significantly reduced the axonal outgrowth capacity of DRG neurons, and methylation at CpG dinucleotides was significantly reduced in the gene body and enhancer regions of *Atf3* following injury (Weng et al., 2017). Thymine DNA glycosylase (Tdg) acts downstream of Tet3 by removing 5-formylcytosine and 5-carboxycytosine, thereby initiating base-excision repair to generate an unmodified cytosine. Weng et al. (2017) found that silencing or conditional knockout of thymine DNA glycosylase also attenuated axon regeneration and reduced RAGs expression. Interestingly, PTEN deletion-induced axon regeneration of mouse RGCs could be attenuated by the silencing of Tet1 instead of Tet3 (Weng et al., 2017).

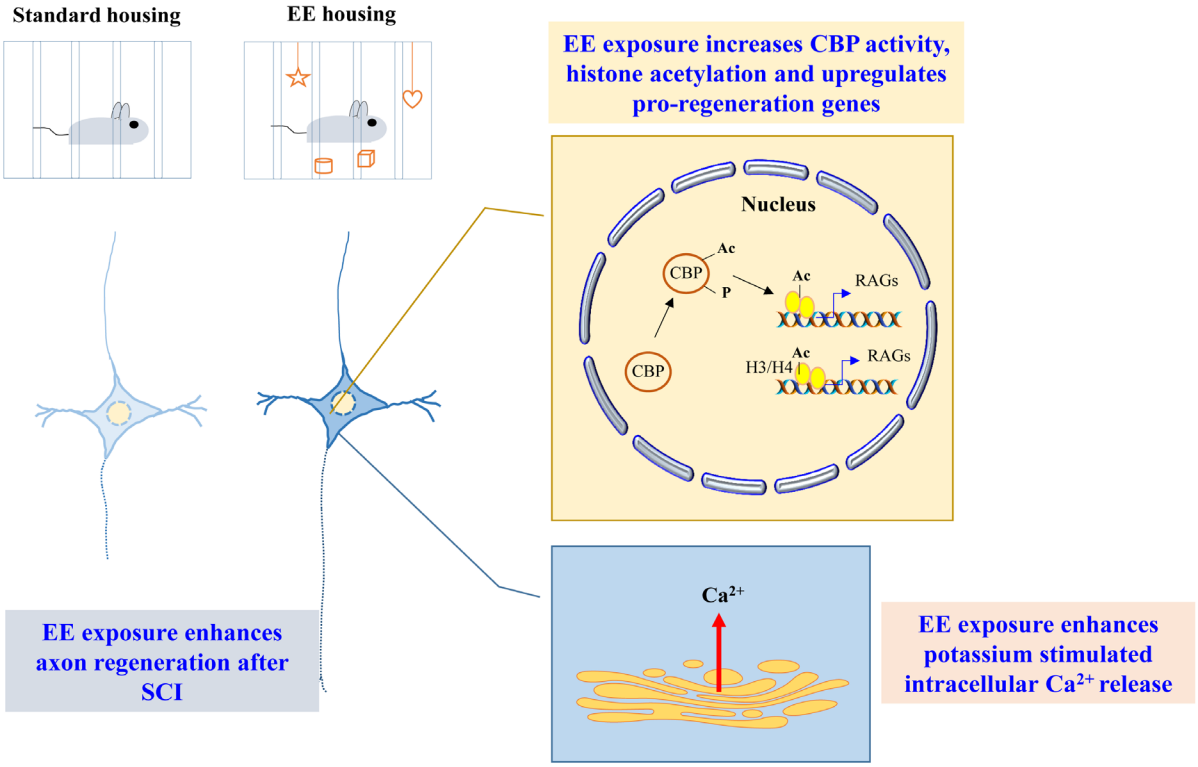

Figure 1 Schematic diagram summarizing the findings of environmental enrichment (EE)-mediated enhancement in axon regeneration of proprioceptive dorsal root ganglion (DRG) neurons.
EE exposure enhanced axon regeneration through EE-elicited neuronal activity resulting in long lasting epigenetic markings in terms of CREB binding protein (CBP)-mediated histone acetylation, which promotes the expression of regeneration associated genes (RAGs). Among the latter are those that promote the ease of Ca^{2+} release with stimuli. Ac: Acetyl group; H3: histone protein 3; H4: histone protein 4; P: phosphorylation; SCI: spinal cord injury.

On the other hand, another report by Oh et al. (2018) found that DNA methylation contributes to robust axon regeneration in the context of specific gene silencing. These authors showed that sciatic nerve injury of DRG neurons reduced the levels of the microRNA miR-9 (Jiang et al., 2017), which in turn resulted in the upregulation of the latter's targets, including ubiquitin-like containing PHD ring finger 1 (UHRF1) and the RE1 silencing transcription factor (REST/NRSF), a master transcriptional regulator of neuron-specific genes (Hwang and Zukin, 2018). The DNA methytransferase inhibitor RG108 reduced the length of axons regenerating though the lesion site. Contrastingly, UHRF1 promoted axon regeneration of DRG neurons. UHRF1 silences gene expression by interacting with dimethylated and trimethylated H3K9, and by recruiting DNA methytransferase1 and DNA methytransferase3a to promote DNA methylation of gene promoters, which include that of PTEN. REST also appears to be important for axon regeneration as its inhibition or silencing both impaired the process in DRG (Oh et al., 2018). Presumably, REST's suppression of neuron-specific genes promoted regeneration by a temporary loss of the terminal differentiation expression profile of adult neurons. However, the role of REST in this regard may be complex as it is itself transcriptionally repressed by UHRF1.

Epigenetic regulatory mechanisms are of course not limited to histone protein acetylation and DNA demethylation. A complex network of miRNAs regulates axonal growth and regeneration (Yoo, 2017), and the roles of a number of different miRNAs in axon regeneration have been extensively described in multiple species (Song et al., 2012; Liu et al., 2013; Gaudet et al., 2016; van Battum et al., 2018; Wang et al., 2018). More recently, Wenk et al. (2018) showed that sciatic nerve injury also elevates N^6-methyladenosine (m^6A)-tagged mRNA or transcripts of RAGs and those that encode components of the protein translation machinery in DRG neurons. m^6A modification of mRNAs is mediated by a methyltransferase complex consisting of methyltransferase like 3 (Mettl3) and Mettl4 (Wang et al., 2016). Conditional knockout of Mettl14 or knockout of the m^6A reader YTH domain-containing family protein 1 attenuated injury-induced translation of proteins in DRGs, reducing axon regeneration as well as associated functional recovery. PTEN deletion-induced axon regeneration of RGC neurons is likewise attenuated by Mettl14 silencing (Weng et al., 2018).

Environmental Enrichment-Elicited CREB-Binding Protein-Mediated Acetylation - Signaling Pathways and Connections

As EE has been previously shown to induce the expression of neurotrophins such as BDNF (Ickes et al., 2000; Rossi et al., 2006; Zhang et al., 2016), a lack of clear elevation of these factors in the Hutson et al (2019) study is mildly surprising. This is particularly so when the mechanism deciphered, CBP activation, is also known to induce BDNF expression (Chatterjee et al., 2013; Palomer et al., 2016). In particular, the use of CSP-TTK21 (Chatterjee et al., 2013) is likely to elevate BDNF expression in the SCI models, and this point would therefore need further confirmation.

CBP is a signal mediated transcription coactivator (Chawla et al., 1998) which has been previously shown to be necessary for EE-induced neurogenesis and cognitive enhancement (Lopez-Atalaya et al., 2011). If CBP activation resulting from neuronal activity elicited Ca^{2+} influx underlies the pro-regenerative phenotype, how is CBP activated by Ca^{2+}? Although not specifically explored by the authors, fundamental mechamisms of neuronal calcium signaling are likely involved. Synaptic calcium influx of from excitatory neural transmission, for example activates synaptic CaMKII (Penny and Gold, 2018). CBP activity is known to be controlled by cAMP, CaMKII and CaMKIV (Hu et al., 1999). CaMKIV could shuttle from the cytoplasm to the nucleus and is a major nuclear CaM kinase (Lemrow et al., 2004). In the context of a pituitary cell line AtT20 (Chawla et al., 1998), nuclear calcium and CaMKIV are the major regulators of CBP/CREB-based transcription. Whether this is the case for DRG neurons remains to be ascertained.

Is the epigenetic mechanism of CBP activation in anyway related to the PTEN-mTOR pathway? Although the work of Hutson et al. emphasized on the role of CBP in histone acetylation, thus affecting axon regeneration via changes in gene expression, it should also be borne in mind that CBP also acetylates PTEN (Ikenoue et al., 2008), and PTEN acetylation is known to attenuate its activity (Okumura et al., 2006) and function (Ikenoue et al., 2008; Tang, 2019). Given that PTEN is a prominent inhibitor of axon regeneration in both PNS and CNS neurons (Park et al., 2010), CBP elevated during injury could conceivably also act through PTEN in terms of promoting DRG axon regeneration. On the other hand, the activity of mTOR, or one of its functional protein complex mTORC1, is essential for axon regeneration, and enhanced mTORC1 activity promotes the latter process (Miao et al., 2016; Carlin et al., 2019). In this regard, EE is known to improve learning and memory in young adult rats (Hullinger et al., 2015) as well as protect against photoreceptor neuron death in Retinitis Pigmentosa (Barone et al., 2012) through mTORC1 signaling. mTORC1 is conventionally consider to function in the cytoplasmic context on organellar membranes, but its non-canonical activity in the nucleus is gaining prominence (Audet-Walsh et al., 2017; Giguère, 2018). Interestingly, CBP has been recently shown to be a substrate of mTORC1, and the latter directly activates CBP by phosphorylation of several Ser residues at its C-terminal domain (Wan et al., 2017). The CBP-based epigenetic enhancement of axon regeneration via upregulation of pro-regeneration genes could therefore cross-talks extensively with the PTEN-mTOR pathway.

Some Caveats and Reservations

The recent findings on how epigenetic mechanisms modulate axon regeneration discussed above provided fresh insights and perspectives on the neuronal intrinsic aspects of axon regeneration upon injury. However, to fully comprehend the

implications of some of these findings would require underlying mechanistic details to be better deciphered. Furthermore, some of the findings also appear, at least superficially, to contradict each other. Several caveats and unresolved issues remain. Firstly, whether DNA methylation is pro- or against axon regeneration appears unsettled, despite the use of similar models. The inferences drawn in different reports at the moment are therefore likely to be context-dependent. Secondly, the role of REST in axon regeneration appears to be complex, and both its levels and its impact on regenerative transcription profile may vary temporarily upon injury. Finally, mechanisms such as CBP-mediated histone acetylation is likely more prominent in some neuronal cell types (such as proprioceptive DRGs) than others. Taken together, the recent findings of epigenetic regulation of axon regeneration should be interpreted with some caution, and should prompt future work. Importantly, despite the above uncertainties, all these findings could have immense translation potential.

Could Environmental Enrichment-Mediated Enhancement in Axon Regeneration be Clinically Useful?

It is a conceivable future prospect that a cocktail of drugs eliciting multiple epigenetic pathways or mechanisms could be used to promote regeneration of injured axons in clinical settings. In terms of EE, clinical implementation has been discussed pertaining to enhancement of recovery from neuronal injuries, such as stroke (McDonald et al., 2018). A number of clinical trials with reasonably positive outcomes have also been reported (Janssen et al., 2014; Khan et al., 2016). However, a lack of qualitative understanding and quantitative gauge of which aspects of EE would be most useful or effective as well as the lack of a clear mechanistic understanding of how EE works, have not helped in its implementation in clinical settings beyond that of general neuro-habilitation. Now, along with the deciphering of the EE elicited, CBP-based histone acetylation mechanism and the somewhat promising efficacy of CSP-TTK21 (Chatterjee et al., 2013) as demonstrated in animal neuronal injury models (Hutson et al., 2019), the time may have come for further human subject-based investigations into EE's use in neuronal injury recuperation settings, and for the development of EE mimetic drugs (Hannan, 2014).

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