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Can chromatin accessibility be exploited for axon regeneration?

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Abstract

Several studies have demonstrated that the intrinsic ability of neurons to regenerate their axons can be stimulated by maneuvers that favor the open state of chromatin, such as inhibiting histone deacetylase activity or increasing histone acetyltransferase activity. Taken together, these experiments suggest that axon regenerative ability can be increased by promoting chromatin accessibility. In this review, we assess the direct evidence in the literature for this hypothesis and re-examine other axon regeneration-promoting manipulations to see if they provide additional support. We find that several interventions known to enhance intrinsic axonal growth capability also increase chromatin accessibility. Although the support for this correlation is strong in the literature, we conclude with a word of caution about therapeutics attempting to exploit this relationship.

Keywords

Epigenetics; PTEN; Neuron; TET3; Neuronal Activity

In eukaryotes, DNA is wrapped around octamers of histone proteins into units called nucleosomes (Luger et al., 1997). Regions not associated with active transcription generally have nucleosomes tightly packed together, limiting access of initiation and transcription factors to the DNA. Thus, active transcription requires that the gene regulatory regions of DNA be made sufficiently accessible (Weintraub and Groudine, 1976). The degree of compaction or accessibility of nucleosomes is correlated with certain post-translational modifications made to the histone proteins (Allfrey et al., 1964; Strahl and Allis, 2000). Acetylation of lysine residues in histone tails by histone acetyltransferases (HATs) decreases the positive charge of the histone tail and thereby weakens the interaction between the histone and DNA, making the DNA more accessible. Conversely, histone deacetylases

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(HDACs) remove the acetyl groups from lysine residues, strengthening the interaction between histones and DNA, thereby making the DNA more condensed (reviewed in (Bannister and Kouzarides, 2011)).

The relationship between chromatin accessibility and axon regeneration

During development, neurons extend axons and innervate their targets, but in adults, neurons of the CNS display a greatly reduced capacity for axonal growth (Huebner and Strittmatter, 2009). A developmental decline has been observed in global histone 3 lysine 9–14 (H3K9-14) acetylation in cortical and cerebellar granule neurons; this decline is temporally correlated with a diminished axonal growth capacity (Gaub et al., 2010). In cortical neurons, a more specific developmental decline in chromatin accessibility was also observed in the promoter regions of several regeneration-associated genes (Venkatesh et al., 2016). In line with these findings, p300/CBP-associated factor (PCAF)-dependent histone 3 (H3) and histone 4 (H4) acetylation was observed to increase in dorsal root ganglion (DRG) neurons following peripheral axotomy (Cho et al., 2013; Finelli et al., 2013; Puttagunta et al., 2014), which produces transcription dependent changes in gene expression that increase the intrinsic regenerative capacity of the neurons (Smith and Skene, 1997). Notably, these changes in acetylation do not occur following central axotomy, which fails to prime the neurons for regeneration (Finelli et al., 2013; Puttagunta et al., 2014). Moreover, PCAF was found to be necessary for the regeneration of a DRG axon's central branch that is produced by a "preconditioning" lesion of DRG peripheral axons in the sciatic nerve (Puttagunta et al., 2014). This evidence reinforces the role of epigenetic regulation in axon growth and indicates a positive correlation between chromatin accessibility and axon growth competence.

Several studies have attempted to test the causality of the relationship between chromatin accessibility and axon growth by modulating the activities of HDACs. The small molecule inhibitor of class I and II HDACs, trichostatin A (TSA), was shown to increase H3K9-14 acetylation and *in vitro* neurite outgrowth in cerebellar granule neurons (Gaub et al., 2010), but, interestingly, failed to promote neurite outgrowth in retinal ganglion cells (RGCs) despite increasing global H3K18 acetylation (Gaub et al., 2011). Cho and colleagues determined that the activity of HDAC5 in deacetylating chromatin was sufficient to repress neurite outgrowth of DRG neurons *in vitro* (Cho et al., 2013). After peripheral axotomy, HDAC5 is exported from the nucleus thereby allowing the increase in H3 acetylation observed in this paradigm (Cho et al., 2013). Once outside the nucleus, HDAC5 deacetylates tubulin at the tips of injured axons which further facilitates growth-cone dynamics and axon regeneration (Cho and Cavalli, 2012; Cho et al., 2013).

In a complementary set of experiments, the relationship between chromatin accessibility and axon growth competence has also been tested by increasing HAT activity. Overexpression of the HAT p300 in adult RGCs promoted axon regeneration after an optic nerve crush, with a concomitant increase in H3K18 acetylation (Gaub et al., 2011). Overexpression in DRG neurons of PCAF, which is required for preconditioning-dependent axonal regeneration, was sufficient to promote regeneration of central DRG axons after a spinal cord injury (Puttagunta et al., 2014).

If increased chromatin accessibility truly promotes intrinsic axon growth capacity, one might expect the effects of known axon growth promoting manipulations to be accomplished, at least in part, by enhancing chromatin accessibility. We examined several well-established means of promoting axon growth to determine whether they have known effects on chromatin accessibility, and whether the observed effects on chromatin accessibility are consistent with the relationship described above.

Many maneuvers that enhance intrinsic axonal growth capabilities also increase chromatin accessibility

PTEN/mTOR signaling

Deletion of the protein/lipid phosphatase PTEN has been consistently observed to promote axon regeneration (Park et al., 2008; Liu et al., 2010; Zukor et al., 2013). A major function of PTEN is to dephosphorylate phosphatidylinositol trisphosphate (PIP3) into phosphatidylinositol bisphosphate (PIP2), thereby antagonizing PIP3-dependent PI3K signaling. The axon regeneration-promoting effects of PTEN deletion have commonly been described as being conveyed by enhancing mTOR signaling (Park et al., 2008).

Until recently, there was no reason to suspect that the axon regenerative effects of PTEN deletion could be mediated through increased chromatin accessibility. In 2014, however, deletion of the C-terminal domain of PTEN was demonstrated to cause genomic instability and tumor development (Sun et al., 2014). A follow-up study found that PTEN directly interacts with histone H1 through its C-terminal domain (Chen et al., 2014). PTEN deletion lead to both decreased binding of H1 to chromatin and increased H4K16 acetylation, thereby promoting chromatin accessibility (Figure 1A). It has therefore been proposed that PTEN is a positive regulator of chromatin condensation (Chen et al., 2014). This conclusion was supported by an independent group of researchers the following year (Gong et al., 2015). PTEN was also recently found to antagonize the insertion of histone variant H3.3, which is correlated with active transcription and accessible chromatin (Benitez et al., 2017). It is unclear whether the effects of PTEN on H1 and H3.3 are related, but in both cases, PTEN expression is inversely correlated with chromatin accessibility.

The ability of PTEN deletion to promote axon regeneration is widely thought to be conveyed through mTOR signaling. mTOR signaling is complex, affecting PI3K, AKT, and S6K signaling, and the mechanisms through which mTOR promotes axon regeneration are incompletely understood (Al-Ali et al., 2017). In addition to this signaling complexity, mTOR may also be localized in the nucleus, where it can promote chromatin accessibility (Tsang et al., 2010; von Walden et al., 2016). This suggests that depletion of PTEN may increase chromatin accessibility indirectly, by enabling increased nuclear mTOR activity. Taken together, these findings suggest that the nuclear roles of PTEN and mTOR should be tested directly for their effects on axon regeneration.

Neuronal Activity

Enhancement of neuronal activity by electrical stimulation promotes axon regeneration, target reinnervation, and functional recovery (Sebille and Bondoux-Jahan, 1980; Nix and

Hopf, 1983; Al-Majed et al., 2000). In a recent study, it was found that stimulating increased firing of RGCs through either visual stimulation or chemogenetic techniques promoted long-distance axon regeneration with numerous axons re-innervating their appropriate targets (Lim et al., 2016). Another group found that overexpression of the light-sensitive GPCR melanopsin in RGCs enhanced the amplitude and duration of their firing in response to light and led to a light-dependent increase in axon regeneration (Li et al., 2016). Similarly, enhancement of neural activity by stimulating Channelrhodopsin2-expressing spinal motor neurons with blue light one hour before nerve injury led to increased target re-innervation (Ward et al., 2016).

Might these effects be linked to changes in the open state of chromatin? Direct measurement of accessible chromatin in dentate granule neurons before and one hour after electrical stimulation-driven neuronal activity revealed widespread changes in chromatin accessibility, with the vast majority (87%) of the differentially accessible regions having increased accessibility (Su et al., 2017). This finding suggests that neural activity-induced promotion of axon regeneration may involve its ability to enhance chromatin accessibility. Consistent with this result, another study found widespread induction of transcription, particularly at enhancers, following neuronal activity (Kim et al., 2010). Su and colleagues further found that the regions of increased accessibility were enriched for the AP-1 motif and that the AP-1 transcription factor c-Fos was necessary to initiate activity-induced chromatin opening (Figure 1B) (Su et al., 2017). This finding is of particular relevance for axon regeneration, because the expression of AP-1 family members is commonly associated with regenerative success (Herdegen et al., 1992; Broude et al., 1997; Lindwall and Kanje, 2005; Michaelievski et al., 2010; Yuan et al., 2012; Chandran et al., 2016). Together, these results suggest a model of neuronal activity-induced axon growth competence where increased chromatin accessibility may be mediated in part by AP-1 transcription factors, and the same transcription factors then promote expression of regeneration-associated genes.

TET Enzymes

Ten-eleven translocation methylcytosine dioxygenases (Tets) are enzymes that oxidize 5-methylcytosine in DNA into 5-hydroxymethylcytosine (5hmc) (Ito et al., 2010; Rasmussen and Helin, 2016). There are three Tet enzymes in jawed vertebrates, TET1, TET2, and TET3 (Ito et al., 2010). The product of Tet enzymatic activity, 5hmc, is enriched in regions of open chromatin (Bhattacharyya et al., 2017) and is the first step in the demethylation of DNA, a key step in activating transcriptionally repressed genes (Figure 1C) (Pastor et al., 2013). TET3 was recently demonstrated to be upregulated in DRG neurons 1–3 days after a peripheral lesion (Loh et al., 2017; Weng et al., 2017). In line with this observation, the product of its enzymatic activity, 5hmc, was globally increased in DRG neurons at the same time points after peripheral lesion (Loh et al., 2017; Weng et al., 2017). TET3 has been demonstrated to be necessary for axon regeneration in DRG neurons with ultimate demethylation of the hydroxymethylated DNA required for at least half of its effect (Weng et al., 2017). Additionally, TET1 knockdown was able to attenuate PTEN deletion-induced axon regeneration in RGCs after optic nerve crush (Weng et al., 2017).

Since demethylation makes chromatin more accessible to transcriptional regulators, these findings can be viewed as another component of the model that chromatin accessibility correlates with axon regenerative potential. However, the chromatin modifying properties of TETs are not limited to their roles in demethylation, as TETs have several functions independent of their catalytic activity. TET2 and TET3 can recruit O-linked β -N-acetylglucosamine transferase (OGT) to chromatin (Chen et al., 2013; Ito et al., 2014). OGT catalyzes the addition of N-acetylglucosamine to serine or threonine residues of cytoplasmic proteins, as well as nuclear proteins such as histones (Hart et al., 2011). OGT has been shown to both stimulate and repress transcription in different conditions. MLL5 (mixed lineage leukemia 5) of the H3K4 methyltransferase MLL family is stabilized by OGT, leading to increased MLL5-mediated chromatin remodeling and transcriptional activation (Zhou et al., 2013). Conversely, OGT can repress transcription through its interaction with PRC2 (polycomb repressive complex 2). Cultured DRG neurons from OGT knockout mice have decreased axonal outgrowth (Su and Schwarz, 2017). This loss in growth competence may be attributed to the fact that TET2 and TET3 co-localize with OGT at active promoters, and a loss in activity of either can lead to a decrease in transcription (Chen et al., 2013; Deplus et al., 2013). Recent evidence also suggests that TET3 can bind to RNA polymerase II, increase chromatin accessibility, and upregulate transcription independent of its catalytic activity or OGT function (Krueger et al., 2017). Although this mechanism is incompletely understood, it could account for some of the effects of TETs on axon regeneration.

Discussion

The concordance of the effects of these disparate regeneration-associated biological processes on chromatin accessibility is striking, and is consistent with a causal role for the opening of chromatin in promotion of axon regeneration. Nevertheless, we are missing key pieces of the experimental puzzle. In many cases, the experimental data discussed here were not generated in neurons, and the responses of injured neurons to the same manipulations could be different. As one example, it would be instructive to compare chromatin accessibility in DRG neurons after peripheral axotomy, when it is expected to increase, with that after central axon injury, when it is not expected to increase.

Despite the overall pattern of a global increase in chromatin accessibility when axon regenerative capability is enhanced, many of the papers examined here report some degree of genomic locus specificity to these epigenetic effects. Unfortunately, we have little clue as to how these processes may be directed to specific loci so as to improve axon regeneration. If new therapeutic strategies are devised to promote axon regeneration by directly increasing global chromatin accessibility, there is a risk that harmful effects may outweigh the beneficial ones. In fact, dysregulated chromatin accessibility is frequently linked to cancer (Wang et al., 2007) and is associated with numerous aging related issues (Rodrigues et al., 2014). It may be that a moderate, targeted increase in chromatin accessibility could re-enable axonal growth competence in mature neurons, but a more widespread increase in accessibility could lead to adverse effects. Finding more targeted and nuanced methods of opening chromatin is the next big challenge for this approach.

List of abbreviations

DRG	Dorsal Root Ganglion
HAT	Histone Acetyltransferase
HDAC	Histone Deacetylase
H3	Histone 3
H4	Histone 4
RGC	Retinal Ganglion Cell
TET	Ten Eleven Translocation Methylcytosine Dioxygenase

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Figure 1: Diagram summarizing the effects on chromatin accessibility of three axon regeneration-promoting interventions.
A) PTEN in a complex with nucleosomes. Deletion of PTEN prevents the binding of Histone H1 to DNA and thereby promotes chromatin accessibility. B) Enhancement of neuronal activity induces expression of AP-1 factors, mediating chromatin opening and activating transcription. C) Overexpression of TET enzymes catalyzes conversion of 5-methylcytosine (5mc) to 5-hydroxymethylcytosine (5hmc), thereby promoting chromatin opening.