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REVIEW

Transcriptional and Epigenetic Regulation in Injury-Mediated Neuronal Dendritic Plasticity

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Abstract Injury to the nervous system induces localized damage in neural structures and neuronal death through the primary insult, as well as delayed atrophy and impaired plasticity of the delicate dendritic fields necessary for interneuronal communication. Excitotoxicity and other secondary biochemical events contribute to morphological changes in neurons following injury. Evidence suggests that various transcription factors are involved in the dendritic response to injury and potential therapies. Transcription factors play critical roles in the intracellular regulation of neuronal morphological plasticity and dendritic growth and patterning. Mounting evidence supports a crucial role for epigenetic modifications *via* histone deacetylases, histone acetyltransferases, and DNA methyltransferases that modify gene expression in neuronal injury and repair processes. Gene regulation through epigenetic modification is of great interest in neurotrauma research, and an early picture is beginning to emerge concerning how injury triggers intracellular events that modulate such responses. This review provides an overview of injury-mediated influences on transcriptional regulation through epigenetic modification, the intracellular processes involved in the morphological consequences of such changes, and potential approaches to the therapeutic manipulation of neuronal epigenetics for regulating gene expression to facilitate growth and signaling through dendritic arborization following injury.

Keywords Nervous system injury · Dendrite plasticity · Transcription factors · Epigenetics

Introduction

The plasticity of dendritic growth and response to injury are surprisingly understudied areas, while the intrinsic and extrinsic factors that affect dendritic growth and targeting during development are more fully understood. Upon injury to the adult central nervous system (CNS) many aspects of development are reintroduced, including the release of glial and neuronal neurotrophic factors [1, 2], morphological and physiological cellular responses to micro-environmental changes, and the structural reorganization of neuronal networks, that provide means of recovery of lost or limited function after injury. At the most basic level, all cells in the CNS respond to extrinsic cues through intracellular signaling cascades that influence cell-specific genes involved in these cellular responses to injury [3]. The involvement of epigenetic changes within neurons, and how they affect neuronal morphology and repair after injury, are now of great scientific interest.

Transcription factors are essential for the initiation of target gene transcription for the further production of transcription factors or the translation of other genes that play roles in the retraction, regrowth, and reorganization of dendritic branches [4–6]. Much of what we know about the

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roles transcription factors play in these processes stem from limited studies on the actions of a handful of key factors. Likewise, the injury-induced plasticity of neuronal extensions is often studied in the context of cellular responses to extracellular events and biochemical interactions that influence neuronal behavior through intracellular signaling cascades and changes in gene expression through epigenetic modulation.

Following CNS injury, the primary mechanical insult and especially the temporo-spatial spread of secondary biochemical inflammatory, oxidative, and other events, cause glial, vascular, and neuronal damage and death surrounding the injury site, [7–9] and induce surviving cells to produce and release a variety of cytokines, chemokines, neurotransmitters, and trophic factors [10–12]. These released agents signal local cells to trigger a variety of responses to the changing microenvironment induced by injury. Glia and neurons secrete powerful trophic factors like glial cell line-derived neurotrophic factor [2], brain-derived neurotrophic factor (BDNF) [12], and nerve growth factor (NGF) [1]. Upon production and secretion into the extracellular matrix, these factors act primarily locally on receptors bound within the membranes of the neuronal soma and dendrites.

Influence of Injury on Dendritic Morphology and Structural Dynamics

After injury to the CNS, local neurons may undergo initial, necrotic, or delayed programmed cell death in response to the primary insult and secondary injury processes. In addition, neurons that do not ultimately die may undergo extensive morphological alterations including dendritic and somatic atrophy [13–16], as well as synaptic and dendritic remodeling [17].

By 1 week after thoracic spinal cord injury (SCI), neurons in the cord show atrophic dendritic arbors in addition to reduced soma size [18]. Several weeks following CNS injury, surviving neurons continue to exhibit the atrophic attributes of reduced dendritic length [19] and soma area. Loss of afferent input to neurons as a result of injury may be the cause of dendritic atrophy following SCI [19], though intracellular signaling and cellular degradation pathways like autophagy are known to be acutely activated [20] and may result in morphological changes.

Transcription Factor Involvement in Dendritic Plasticity

Research over the past decade has uncovered many mechanisms by which dendrites grow and dendritic fields are maintained. Different neuronal types exhibit different morphologic orientations of dendritic patterning likely based on their location, local microenvironment, and function within the CNS. This knowledge is important for understanding the dendritic response to injury, as well as appreciating particular responses to pharmacological or other agents aimed at modulating neuronal morphology and plasticity to improve repair and recovery in trauma and disease. Investigations into the genetic influence and types of transcription factors that regulate the intrinsic capacity of neurons to grow and respond to extrinsic stimuli have been pivotal to broadening knowledge of these topics.

Much work in answering basic questions regarding transcription factor control over neuronal morphological plasticity has involved studies using *Drosophila* as a model, especially concerning dendritic regulation. As the *Drosophila* nervous system is simple compared to vertebrates, primary transcriptional mediators of neuronal fate and dendritic patterning have been successfully identified. The development of subclasses of multipolar dendritic neurons is controlled by a combination of key transcriptional regulators. These dendritic arborization (da) neurons appear to be coordinated in development to some extent by the level of *cut* gene expression [21]. Cut is a homeodomain protein and transcription factor involved in regulating the complexity of dendritic arbors [21]. Neurons with small and non-complex dendritic arbors express no Cut (Class I) or low levels of Cut (Class II). Higher expression levels of Cut result in increasingly greater complexity of dendritic fields (Classes III and IV) [22, 23]. The mammalian version of Cut, known as CCAAT-displacement protein (CDP), is interchangeable with Cut in *Drosophila* neurons with similar results [22]. CDP, also known as Cux1, is located in mature cortical pyramidal neurons among other neurons of the mammalian CNS [24], where it is suggested to modulate the post-mitotic morphological characteristics of neurons including dendritic patterning. Cut may stimulate the development of actin-rich filopodia-like extensions that may contribute to dendritic branching dynamics. Part of this influence could stem from its inhibition of p27Kip1 expression and modulation of RhoA signaling [25].

Another transcription factor studied in *Drosophila* that is conserved in mammals is the protein Abrupt. Abrupt is a BTB-zinc finger protein of the Knot/Collier family of proteins that contributes to the transcriptional regulation of dendritic arborization in class I da neurons [26–28]. Specifically, Abrupt dose-dependently diminishes dendritic branching [27], thereby likely coordinating with Cut to establish the class I-specific lack of a dendritic arbor in post-mitotic neurons. However, any role of potential mammalian homologs of Abrupt remains unclear. Another transcription factor that influences dendritic complexity in *Drosophila*, Spineless, has a mammalian homolog, aryl-hydrocarbon (dioxin) receptor (AHR); however, AHR does

not appear to affect dendritic development in mammalian neurons the way it does in *Drosophila* [29].

Though somewhat less understood, other transcription factors play known roles in the dendritic patterning of mammalian neurons. Evidence suggests that the basic helix-loop-helix transcription factors neurogenin-2 and NeuroD affect dendritic morphological organization in cortical pyramidal neurons and granule neurons, respectively [30–32]. Others, such as activating transcription factor-3 (ATF-3) and signal transduction and transcription-3 (STAT3) are better characterized and induce a variety of responses in neurons during development and in response to injury and treatment.

ATF-3 is a transcription repression protein, targeted by neuronal cyclic AMP-response element binding (CREB) protein signaling, that promotes neuroprotection and prevents the dendritic damage caused by neurotoxicity and the oxygen-glucose starvation induced by ischemic injury [33, 34]. It is known that ATF-3 regulates gene expression through dimerizing or interacting with other transcription factors in the leucine zipper family like Fos/Jun [35, 36], which allows binding to Ap1 and CRE/ATF promoters [37, 38]. Upon injury, ATF-3 is upregulated in many neurons in the CNS [39, 40] and peripheral nervous system [41, 42]. Upon overexpression, ATF-3 stimulates enhanced neurite outgrowth *in vitro*, suggesting that the transcription factor increases growth plasticity in neurons, although the exact transcriptional mechanism remains unclear. Some genes regulated by ATF-3 in neuronal cells include heat shock protein 27 (Hsp27) [43] and c-Jun [38], the latter of which is involved in ATF-3-mediated neurite growth [44]. It could be that ATF-3 acts in concert with other transcription factors and modulates the expression of various genes to stimulate such neuronal responses. The mechanisms by which ATF-3 regulates neuronal responses to injury and regrowth require further study.

STAT3, among other members of the STAT transcription factor family, isalso induced by injury to the nervous system [45, 46]. *In vitro* and *in vivo* evidence suggests that activation of STAT3 by phosphorylation at Tyr 705 is protective in injured neurons [45, 46]. Phosphorylation of STAT3 and other STAT proteins occurs primarily through the activation of Janus kinases (JAKs) by cell receptor binding by neurotransmitters, hormones, neurotrophic factors, or other extracellular signaling proteins. A primary cellular function for JAK-STAT signaling is to influence gene expression [47]. Upon activation, JAKs are phosphorylated and this leads to the phosphorylation and dimerization of STAT proteins. STAT dimers localize to the nucleus, bind DNA, and serve in the regulation of gene transcription. Among the many physiological functions of JAK-STAT signaling are cell survival [48, 49], axon growth [50], differentiation, and proliferation [51, 52]. After CNS injury, JAK-STAT signaling and STAT3 expression appear to play roles in neuronal plasticity and regrowth. Specifically, upon neurite damage, STAT3 expression and activity increase in regenerating neurons [53]. STAT3 activation is also involved in neuronal differentiation and neurite outgrowth in the presence of trophic factors, including NGF and BDNF [54]. STAT3 activation by Trk receptor-activation by neurotrophins may be a point of interaction between multiple intracellular signaling pathways, including phosphatidylinositol-3-kinase (PI3K) and extracellular-related kinase (Erk) in addition to JAK signaling [54].

Epigenetic Modifications Following Central Nervous System Injury

In normal CNS development and function, appropriate gene expression through epigenetic regulation is of great consequence. Even minor fluctuations in neuronal activity can, and may be necessary, to impart extended modification of gene expression [55]. As such, when insulted by trauma or through other means, dramatic changes in intraneuronal processes occur that can result in chronic dysregulation of function and altered neuron metabolism, and can instigate necrotic and programmed cell death. The term "epigenetics" is traditionally applied to the system of regulation of heritable changes of gene expression separate from those ofDNA itself. However, epigenetics now covers a broad set of processes and events that regulate chromatin structure and function. Non-replicating neurons are unique in that epigenetic modifications are not inherited. Therefore, the specific term "neuroepigenetics" has been suggested to cover such epigenetic events that occur within the CNS [56].

After injury to the brain or spinal cord, projections of neurons involved in neuron-neuron interaction and communication as well as the surrounding glia are lost or damaged. In cells that survive the initial trauma, a complex orchestration of events involving histone-modifying enzymes and transcription factors unfold to mediate drastic changes in gene expression that allow for the specific cell type to respond to temporal changes in tissue pathology post-injury. Chromatin remodeling is highly important in the regulation of neuronal degeneration, plasticity, and regrowth by controlling critical transcriptional processes in neurons and glia [57–59]. In general, at least 8 major epigenetic modifications affect chromatin remodeling in cells (Fig. 1).

Some of the best-studied enzyme-mediated epigenetic responses include histone lysine acetylation and deacetylation [60]. The acetylation of lysine residues on histone N-termini is accomplished *via* the activity of histone acetyl

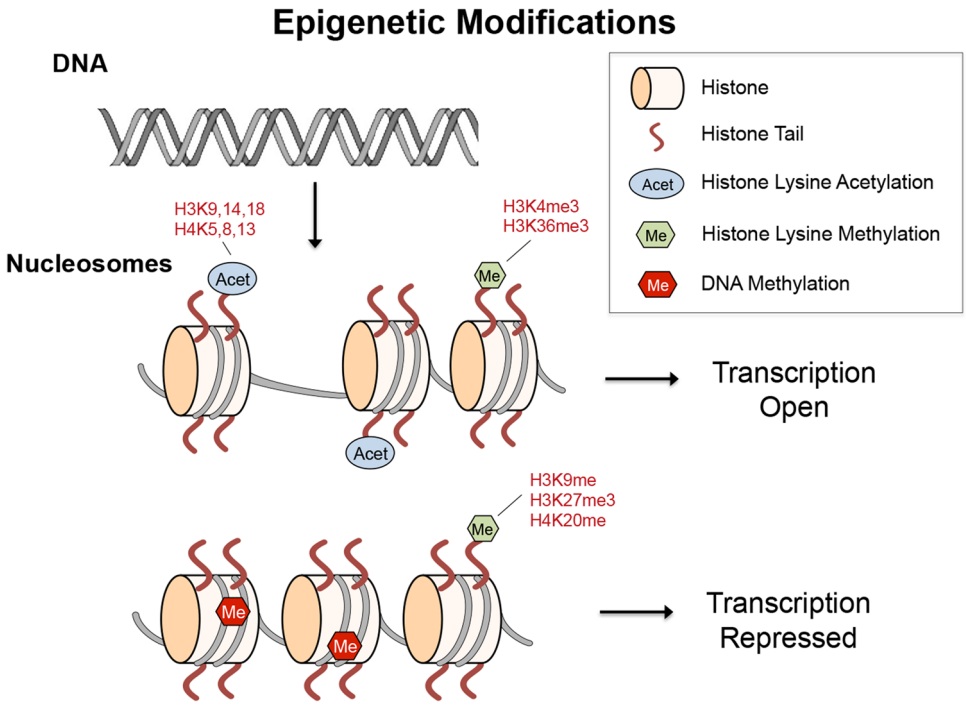

Fig. 1 Cartoon of general cellular epigenetic modifications and transcriptional outcomes. Examples of histone lysine acetylation and methylation sites associated with transcriptional regulation are labeled in red.

transferases (HATs). Histone acetylation by HATs neutralizes the positive charges on histone tails that promotes chromatin unfolding and enhances access of the transcription factors involved in gene regulation. Alternatively, histone deacetylases (HDACs) eliminate these acetyl groups, compress chromatin, and repress transcription. As described in a recent review by Lv *et al.* [61], overall spinal cord levels of acetylation are downregulated in rat models of SCI, and giving valproic acid (VPA), a class I HDAC inhibitor, increases acetylation and enhances the recovery of function [61–63]. Whether or not these effects of VPA are the result of the direct influence on chromatin modification is unclear, as VPA modulates various intracellular signaling pathways and has its own neuroprotective effects [64]. Nevertheless, the evidence suggests that epigenetic modulation through increased histone acetylation has a positive influence on the functional ability and other effects of various cellular events in animal models of SCI.

The role of Class II HDACs, including HDAC4, 5, 6, and 7, is less understood. However, research suggests that specific Class II HDACs have a positive impact on specific neuronal functions and synaptic plasticity. Knock-out of HDAC4 in mice reduces hippocampal neuron functions and synaptic plasticity, negatively impacting learning and memory [65]. Interestingly, HDAC5 knock-out doesnot have similar effects, suggesting HDAC-specific influences on neuronal behavior and morphology. Such findings have important consequences for the development and application of therapeutics targeting HDAC activity and epigenetic regulation. It would appear that broadly targeting HDAC inhibition after CNS injury should be cautioned against, as increased activity in some HDACs, such as those in Class I, may be detrimental while some Class II HDACs may prove beneficial when active in certain neuronal populations. As Class II HDACs are known to be activated *via* Ca^{2+} signaling in neurons, and such signaling is a well-understood process in neuronal responses to brain and spinal cord injury, a better understanding of HDACs and other epigenetic modulators is needed for optimal therapeutic development for modifying such events under these pathological conditions.

Another prominent epigenetic alteration involves direct DNA modification by chemical methylation [66]. DNA methyltransferases (Dnmts) are responsible for DNA methylation through methyl group transfer from *S*-adenyl methionine to a cytosine residue to form 5-methylcytosine. During DNA replication, Dnmt1 regulates transfer of the DNA methylation pattern from the parent DNA strand to the new daughter strand. Other Dnmts, Dnmt3a and Dnmt3b are known as *de novo* Dnmts as they set in place new patterns of methylation of unmodified DNA [67]. In mature post-mitotic cells, such as CNS neurons, Dnmt expression is downregulated but still expressed, which suggests a role in CNS neuronal functions [68, 69]. In fact, some of the highest DNA methylation levels occur in brain tissue [67].

Crosstalk between DNA methylation mechanisms and histone modifications also occur in regulating transcription. As noted earlier, epigenetic modification of histones that cause loosening of histone-associated DNA, such as

acetylation of the N-terminus of histone tails, enhance transcriptional access by transcription proteins and machinery, and Dnmts can interact with histone-modifying enzymes to repress the expression of genes. For example, Dnmt1 and Dnmt3a have been observed to interact with and bind the histone methyltransferase SUV39H1 that methylates histone 3 and lysine 9 (H3K9) and reduces gene expression [70]. It has also been shown that Dnmt1 and Dnmt3b bind HDACs to repress transcription in associated DNA regions through enhanced DNA compaction and by repressing access by transcriptional proteins [71]. Overall, the relationship between Dnmts and histone-modifying enzymes generally results in the transcriptional repression of specific DNA regions.

Experimental traumatic brain injury (TBI) modifies the distribution and expression of Dnmt1, as well as DNA methylation at both the cellular and organ levels [72, 73]. A recent study suggests that DNA hypomethylation and hypermethylation changes occur in both neurons and glia. These changes appear to be dependent on specific DNA regions, and thus the gene regions with which the methylation patterns are associated. In specific neuronal populations, epigenetic changes in Dnmt expression and DNA methylation as well as HDAC expression have been documented, which suggest subpopulation-specific neuronal responses to blast-type brain injury [72, 74]. Blast-injury, among other forms of experimental TBI, causes mild forms of brain damage and diffuse axonal injury. A recent study has shown that controlled cortical impact injury causes local as well as widespread cortical neuronal dendrite degeneration and loss [75]. The mechanisms underlying such events are not well understood, but may, at least in part, result from intracellular transcriptional modulation due to epigenetic changes induced by injury.

Additional extrinsic factors in the CNS may also influence neurite plasticity, both during development and following injury. Recent research has demonstrated an increase in Nogo-A, a myelin-associated molecule, following mild TBI [76]. Nogo-A is best known for its inhibitory effects on axonal and dendritic arbor growth and plasticity [77, 78]. The upregulation of Nogo-A has been implicated in the inhibition of axonal arborization in a stroke model of brain injury [79]. Its action in these models may serve to stabilize hippocampal dendrites and axons following insult [80]. Nogo-A exerts its effects through binding and stimulating intracellular signaling events through Nogo receptors (NgRs) [81]. Evidence suggests that NgRs also play a role in dendritic plasticity, recent research showing that loss of NgR2 modifies the dendritic spine morphology of pyramidal CA1 neurons [82], which can be damaged following TBI. NgRs act to modify cytoskeletal organization *via* activation of the RhoA family of GTPases [83]. These GTPases, especially Rac1, are known to play roles in dendritic plasticity mediated through epigenetic modifications [84, 85]. Rac1 controls dendritic spine plasticity under normal conditions through cofilin interaction and the modulation of actin polymerization within the spines, and reduction in Rac1 by epigenetic changes, likely through H3K9 and H3K27 methylation [86], increases plasticity by dysregulating this process [85]. Given that Nogo can influence such downstream processes, future research into the influence of Nogo expression and activity on epigenetic modifications in injured neurons will be an area of particular interest.

Cell Signaling, Epigenetics, and Transcription Factors Involved in Dendrite Morphology and Function

Of the various transcription factors that play roles in neuronal structural stability, degeneration, and repair, only a few have been studied in the context of epigenetic modification-mediated effects on dendritic morphology. In particular, the events surrounding intracellular signaling cascades and transcription factor modulation have received the greatest emphasis. Due to the long history of assessment of their influence on neuronal morphology and behavior in normal and pathologic conditions, neurotrophins have often been used in and linked to research on the progression and outcome of transcriptional and epigenetic events that affect dendritic plasticity in neuronal populations.

A prime example, BDNF, has long been associated with neuritogenesis and dendritic plasticity [87, 88]. In addition, BDNF exhibits extensive transcriptional control throughout neurons and locally within the dendrites and spines, which can have important effects on dendritic and synaptic plasticity [89]. BDNF enhances the growth of proximal dendrites through transcriptional modulation by CREB [90]. MAPK signaling appears to be important in the activity of BDNF in this context. BDNF also regulates the transcription of immediate-early genes in central neurons and CCAAT/enhancer binding protein (C/EBP)-NeuroD transcription factors, which influence dendritic differentiation [91] (Fig. 2). Knock-down of TrkB/C or C/EBP retards dendritic maturation, indicating that BDNF signaling *via* this transcriptional mechanism is critical for the proper development of dendritic arbors [91].

Conversely, endogenous transcriptional regulation can also influence BDNF expression and local physiological and morphological effects on neurons. Endogenous BDNF is known to play a role in the regulation of pro-growth and plasticity programs within normal, injured, and developing neurons [92, 93]. Recent research has shown that the epigenetic chromodomain protein and transcription corepressor

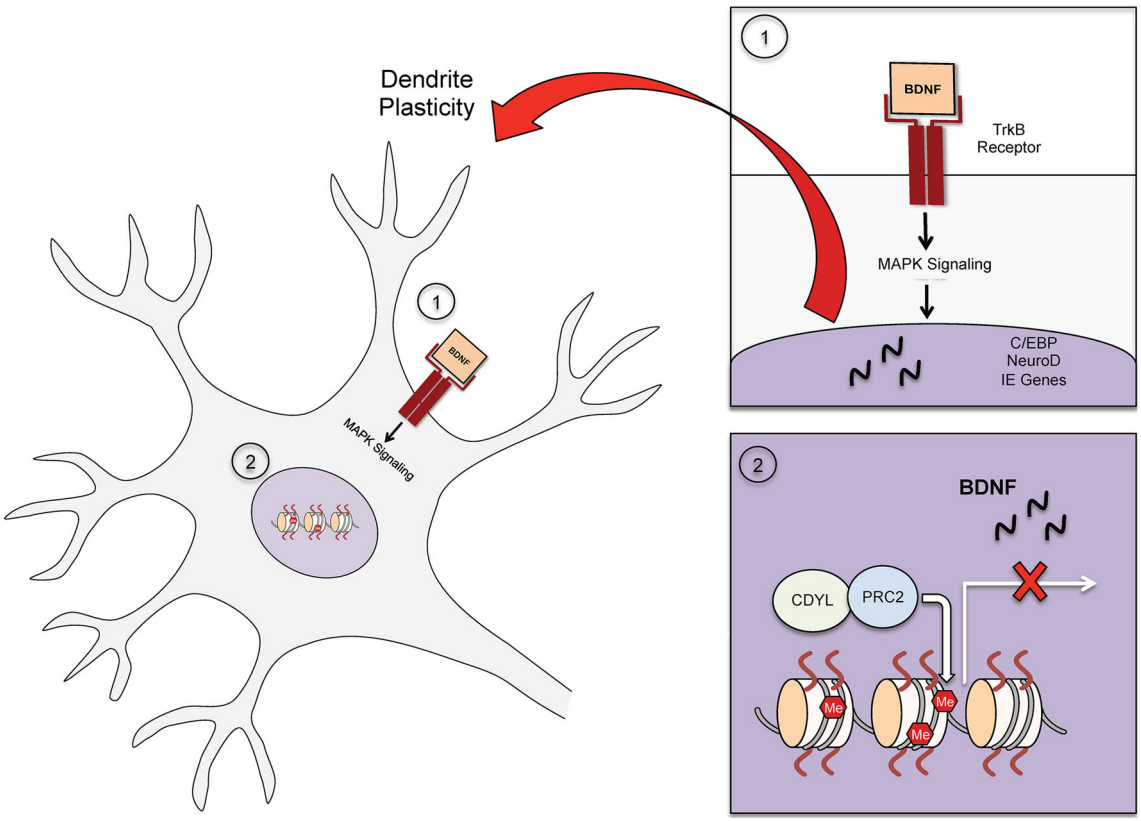

Fig. 2 Examples of extrinsic and intracellular transcriptional regulation of neurotrophic influence on dendritic morphology. (1) BDNF can signal through MAPK and other mechanisms to promote transcription of immediate-early (IE) genes, and transcription factors such as NeuroD to mediate dendrite morphological plasticity. (2) Transcriptional regulation through epigenetic modulation of BDNF that could influence dendritic plasticity.

chromodomain Y-like (CDYL) protein negatively regulates the transcription and expression of BDNF, which directly influences the extent of dendrite morphological change [94]. Evidence suggests that CDYL interacts with the catalytic subunit EZH2 of the partner factor, polycombrepressive complex 2, to recruit H3K27 methyltransferase to the BDNF promoter to mediate this inhibition (Fig. 2). Like other epigenetic methylation processes, this series of events leads to reduced BDNF transcription and expression. Other recent studies have demonstrated that acetylation at lysine 9 of histone 3 by the HAT p300/CBP-associated factor (P/CAF) near the promoter of the *bdnf* gene increases its expression, and this action is associated with a regenerative response in injured neurons [95]. Supporting such a role, pharmacological inhibition of HDACs is followed by a concomitant elevation in P/CAF activity, leading to increased neurite outgrowth [96]. Aside from the influences of direct insult on neurons, specific activity-associated dendritic plasticity, such as that suggested to occur during post-traumatic stress disorder, can also be induced in neurons by epigenetic modifications that alter BDNF expression [97]. Taken together, neuronal transcriptional regulation both by and of BDNF are likely important for overall dendritic growth, maturation, and plasticity.

Aside from the influence of neurotrophins on transcriptional effects involved in dendritic plasticity under stress, other studies have focused on the link between intracellular signaling pathways, transcriptional regulation, and epigenetic modification. Still, the evidence available in the literature linking epigenetics to neurite growth and plasticity is limited. Some evidence suggests that epigenetic factor interactions can regulate the post-translational modification of proteins such as histones, which can impact neurite properties and processes.

DNA methylation in the brain is elevated following ischemia, while downregulating Dnmt1 and reducing DNA methylation appear to confer neuroprotective benefits under these conditions [98, 99]. Application of the neurotrophin NGF stimulates neurite outgrowth from rat pheochromocytoma (PC12) cells *via* Dnmt3b recruitment of HDAC to the T-cadherin promoter [100]. As T-cadherin negatively controls neurite growth, this reduces T-cadherin expression and promotes neurite growth [101]. As such, it appears that Dnmts can influence histone post-translational

modification and subsequently, neurite outgrowth; however, more details and broader implications of such possibilities require further investigation in the context of *in vivo* neural injury models.

After SCI, the levels of Dnmt3a, Dnmt3b, and DNA methylation are decreased in the spinal cord, but are elevated by administration of folic acid, a promoter of neurite growth and a source of methyl groups for Dnmts [102]. This indicates that folic acid-mediated regeneration may occur through DNA methylation. The mechanism underlying this requires further research. Other evidence also suggests a possible role for elevated DNA methylation mediated by folic acid following SCI; this lends support to a proposed mechanism of epigenetic hypermethylation-mediated neuronal regeneration [103]. This is interesting, as DNA hypermethylation is mainly linked to the repression of gene expression.

Whole tissues were used in the *in vivo* studies above, which means that the observed methylation outcomes could have resulted from glial cells rather than neurons. As glia and immune cells are prime players in CNS injury responses, DNA methylation in such cells could influence damage from inflammation and the immune response and the reduced ability of neurons to regenerate [104]. Also, such results could be explained by a spatiotemporal difference between brain and spinal cord neuronal responses to differing injuries. Such variables need to be investigated further to better clarify the role of glial cells, and injury- and tissue-specific neuronal responses in modulating epigenetic events that affect axon and neurite outgrowth. As discussed, transcription factors require access to gene promoters to function in gene expression regulation, and many are known to be directly or indirectly involved in dendrite and neurite plasticity. Epigenetic changes that result from injury or therapeutic modalities certainly impact the ability of transcription factors to access and influence gene expression, and affect feedback and feed-forward mechanisms for further transcription factor and neurotrophin production that can promote dendrite and synaptic plasticity. The coming years will yield exciting results that will expand our understanding of how these varying complex processes in the nervous system interact to influence the dynamics of dendrite plasticity in neural injury and disease, and as importantly, how these dynamics can be accounted for in optimizing therapeutic development and application.

Conclusions and Future Directions

As shown in this review, understanding the gene expression and transcription factor responses of neurons to injury and neurotrophic therapy could help optimize such treatments by providing a foundation for predicting upstream translational and post-translational events that could lead to effective dendritic plasticity and establish functional interneuronal signaling after CNS injury. In many ways, our understanding of the dendritic responses to injury and treatment is relatively immature compared to that available on neuroprotection and axonal regeneration. This is especially true concerning the epigenetic modulation and regulation of gene transcription and the specific influences of these events in neurons, as well as in glial cells that may affect neuronal morphology following CNS injury. In the coming years, a clearer picture of key epigenetic and transcriptional events and regulators will unfold, and this will help to connect our understanding of trophic signaling in neurons and the intracellular signaling cascades that help modulate cytoskeletal and morphological plasticity in affected neurons after CNS injury. During this period, the development of new ideas and potential methods of treatment, including small-molecule mimetics of neurotrophins, may improve the efficacy of inducing neuronal dendritic arborization and protection against dendritic atrophy. The study of dendritic plasticity in the CNS following injury and treatment has come a long way in the last few decades, but still has some way to go until we can effectively use the knowledge for therapeutic means.

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