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Epigenetic changes following traumatic brain injury and their implications for outcome, recovery and therapy

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Abstract

Traumatic brain injury (TBI) contributes to nearly a third of all injury-related deaths in the United States. For survivors of TBI, depending on severity, patients can be left with devastating neurological disabilities that include impaired cognition or memory, movement, sensation, or emotional function. Despite the efforts to identify novel therapeutics, the only strategy to combat TBI is risk reduction (helmets, seatbelts, removal of fall hazards, etc.). Enormous heterogeneity exists within TBI, and it depends on the severity, the location, and whether the injury was focal or diffuse. Evidence from recent studies support the involvement of epigenetic mechanisms such as DNA methylation, chromatin post-translational modification, and miRNA regulation of gene expression in the post-injured brain. In this review, we discuss studies that have assessed epigenetic changes and mechanisms following TBI, how epigenetic changes might not only be limited to the nucleus but also impact the mitochondria, and the implications of these changes with regard to TBI recovery.

Introduction

Epidemiological data from the Centers for Disease Control and Prevention show that moderate to severe traumatic brain injury (TBI) affects nearly half a million individuals per year and accounts for a third of all injury-related deaths. Additionally, mild TBI is estimated to affect between 1.8 and 3.5 million individuals a year in the U.S., with 20% of those progressing to chronic disability. Current models suggest that mild TBI (e.g. concussion) is related to diffuse axonal injury [46]; while moderate to severe include this pathology plus focal damage [67]. Brain protection and repair for TBI are evolving, but there is a great room for target identification leading to new therapeutic approaches to promote better outcomes of TBI that includes, but not limited to, increasing cognitive function, increasing

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the quality of life and more recently, decreasing risk of developing dementia and Alzheimer's disease [66].

Pre-clinical optimism in finding the biological and/or technological 'magic bullet' in the past has not been successfully translated in clinical settings. The robust gap in this translation (and thus the need for 'translational science') is largely a reflection of the heterogeneous and complex nature of TBI: it can vary in location, severity, duration, and symptoms. The pathophysiological mechanisms of TBI are two-fold: 1) primary insult as a result of direct mechanical forces, and 2) secondary insult that involves the damage and loss of neurons [68]. While there is an unprecedented and continual need for preventive and protective measures that can avoid TBI and/or decrease the severity of the primary injury respectively, there is also a great demand to limit secondary brain damage. Although the push for better understanding of TBI and its symptoms has been substantial in the past few decades, the epigenetic aspects of TBI remain relatively unexplored.

Epigenetics refer to functional changes to the genome that alter gene expression, but do not change the underlying DNA sequence [97]. These changes may be rapid and dynamic, or long lasting and heritable through successive cell generations [45]. The primary epigenetic mechanisms often considered to involve DNA methylation, histone modifications including methylation and acetylation, and post-transcriptional mechanisms of regulation through small noncoding RNAs. Although the field of epigenetics is now well established, interest in the epigenetic mechanisms involved in TBI pathophysiology has only recently gained traction. Indeed, recent reviews in CNS injury support the relevance of epigenetics in this field, but these largely focus on pathophysiology of stroke [28, 30, 76] and spinal cord injury [104]. Moreover, our widening understanding of epigenetic changes associated with neural plasticity, learning and memory (reviewed in [100]) reinforces the prospect that understanding the structural and functional changes that occur following TBI could provide innovative approaches to TBI recovery and rehabilitation. In this review, we discuss the available evidence supporting epigenetic mechanisms that are altered, and in some cases, persist following TBI. We also discuss how epigenetic changes might not only be limited to the nucleus, but also impact mitochondria, with emphasis on implications for bioenergetics in TBI recovery. This is an emerging area of study, which has the potential to offer important and novel insight into the biology of regeneration and recovery after TBI.

Traumatic Brain Injury

TBI is an incredibly complex process, and therefore any discussion of underlying mechanisms requires a good framework. TBI can be categorized into two main, but not necessarily exclusive, types: focal and diffuse. Focal TBI's involve direct impact on the brain (e.g. blow to the head, a fall, or bullet wound entry). Depending on the severity, bruising of the brain (contusion) could often occur, as well as intracranial bleedings (e.g. subarachnoid hemorrhage, subdural hematoma)[68]. Focal injury often results in excessive and pathological release of excitatory neurotransmitters, in particular glutamate, leading to excitotoxicity due to influx of calcium and sodium ions [13, 14]. For this reason alone, blocking of voltage-gated calcium channel improves behavioral outcome in rats after TBI [57]. Moreover, disruption of cytosolic calcium is associated with increased mitochondrial

dysfunction, where TBI in rats saw an excessive absorption of calcium to the mitochondrial membrane, leading to the inhibition of electron transport chain and energy transduction [103].

On the other hand, diffuse injury does not need direct impact to the brain. Concussion, although minor in severity, is one of the most common types of diffuse TBI and it is often caused by motor vehicle accidents [23]. Here, rapid rotational acceleration and deceleration forces to the brain lead to diffuse axonal injury; including in severe cases, axonal shearing [29]. The axons are stretched causing a dramatic cytoskeletal deformation that ultimately interrupts axonal transport, resulting in accumulation of transported materials in axonal swellings, or varicosities, within just hours of trauma [90]. Commonly varicosities appear in a periodic arrangement along the length of an axon at the site of injury, and can be reproduced experimentally using an *in vitro* model of dynamic stretch in axons [94]. This cellular process compromise the transport of crucial axonal cargos such as the mitochondria, and in diffuse axonal injury states, these components accumulate at the varicosities. Another axonal pathology found in diffusely injured white matter is a large single swelling described as an axonal bulb (previously referred to as a retraction ball) [63–73], which likely represents complete axonal disconnection [49–75].

While the primary consequence of diffuse axonal injury revolves around mechanical and cytoskeletal perturbations, secondary consequences are equally detrimental to the recovery of axons. Specifically, changes in mitochondrial integrity, movement and bioenergetics can alter the course of repair [7–32–52–53–60–63–73–81]. Mitochondria are considered the powerhouse organelle of the cell, where they play a critical role in cerebral metabolism through the process of oxidative phosphorylation, which drives the production of ATP. They also play a pivotal role in the regulation of oxidative stress, excitotoxicity, and apoptosis [83]. These organelles are motile, and depend on microtubule transport to move to areas of high-energy demand in the neuron [85]. In fact, the precise location of mitochondria is important and they have been shown to be preferentially, and strategically, located in the internodes where the energy-dependent Na^+/K^+ ATPase resides [71–107]. Given that axons are high-energy demanding regions of the neuron, where ATP is vital for the rapid propagation of action potentials and survival, it is not surprising that there is a correlation between the degree of mitochondrial dysfunction and recovery following TBI [60–61–72–89–91].

Neuroepigenetics

DNA and Histone Methylation

DNA methylation is one of the best-studied epigenetic mechanisms to date, in which methyl groups are added to the cytosine base within cytosine–guanine dinucleotides (CpG sites) [42]. The modification is carried out by a family of DNA methyltransferase enzymes (DNMT1, DNMT3a, and DNMT3b) and often occurs at or near 5' promoter sites where CpGs are frequently clustered in high density [70]. Although DNA methylation was once thought to be an inherently stable mark, recent findings have shown that it is more dynamic than previously recognized, with demethylation occurring via the activities of ten-eleven translocation enzymes (TET1, TET2, and TET3) [39–47–48] and thymine-DNA glycosylase

[39]. Methylation has long been appreciated as an effective means of gene silencing as hypomethylation of CpGs occurs at most actively transcribed genes, whereas hypermethylation of promoters results in gene repression [10, 33, 93]. DNA methylation at promoter CpG sites leads to the repression of gene expression by altering the conformation of DNA itself and local histone structures [19, 70].

Although alterations in gene expression have been observed in different TBI models [24, 36], only a few studies to date have directly investigated the role of epigenetic modifications. One study, in which DNA methylation changes were examined early following contusion TBI in rats revealed that global hypomethylation is seen early (day 1 post injury) in regions of widespread necrosis, and slightly delayed in more peripheral regions (day 2 post injury) [108]. Further analysis shows that hypomethylation was occurring mainly in activated microglia/macrophages, suggesting hypomethylation defines a sub-population of microglia/macrophages involved in the early processes following TBI. Schober *et al.* have also reported global DNA hypomethylation in the 17-day-old rat brain following controlled cortical impact TBI [86]. However, when examining a specific gene locus, IGF-1, in the hippocampus it was found that TBI was associated with DNA hypermethylation at one region within the gene (exon 5 and upstream), and DNA hypomethylation at another (downstream of exon 5). The temporal epigenetic changes correlated with the expression of IGF-1 and the splice variant, IGF1B [86], which have been shown to play important neuroprotective roles in the brain's endogenous response following TBI [43, 51, 82, 84].

Cell-specific DNA methylation perturbations in neurons and glia associated with TBI have also been identified in an animal model of blast overpressure (Table 1). These methylation perturbations appear to be sustained months following blast exposure, suggesting that DNA methylation alterations attributed to blast injury can persist long term [37]. Interestingly, these data identified DNA methylation alterations in a number of genes and genetic pathways previously implicated in TBI, and related neurological and neuropsychiatric disorders. Most notably, genes involved in sleep regulation, including *Aanat*, *Nos1*, *Il1r1*, *Homer1*, *Chrna3* and *Per3*, all showed increased DNA methylation and modest decreases in gene expression in the brains of blast exposed animals [37]. Sleep disturbances are common following TBI, and occur frequently in war veterans who have sustained TBI [12, 18, 74, 96].

While these studies demonstrate DNA methylation changes in response to TBI in animal models, the cause of DNA methylation changes following injury have only recently begun to be identified. An in-depth study into the transcriptional expression patterns of the enzymes responsible for controlling DNA methylation and demethylation has shown that different levels of blast injury may trigger distinct pathways in specific brain regions, and produce different cellular responses to the injury [4]. Expression changes were observed in enzymes controlling DNA methylation, such as DNMTs, TETs and thymine-DNA glycosylase (TDG). The hippocampus was more vulnerable to enzyme expression changes than the prefrontal cortex, which correlated with aberrant DNA methylation [4]. A significant negative correlation was found between global DNA methylation and the magnitude of blast overpressure exposure. It is thought that altered DNA methylation patterns may offer insight into the characteristic outcomes associated with the injury pathology including

inflammation, oxidative stress and apoptosis [4]. As such, these enzymes will be important targets for future therapeutic intervention strategies.

Histone Acetylation

Other well-studied epigenetic mechanisms include post-translational modification of histone subunits, with which DNA associates in the form of nucleosomes [2]. There are many types of reversible covalent histone modifications such as lysine acetylation, lysine and arginine methylation, serine and threonine phosphorylation, lysine ubiquitination, poly-ADP ribosylation and sumoylation [8]. Methyl groups are added to, or removed from lysine residues by histone lysine methyltransferases (HKMT) or demethylases (KDM), respectively and added to arginine residues by protein arginine methyltransferases (PRMT) [8]. By contrast, acetyl groups are added to or removed from lysine residues by histone acetyltransferases (HATs) and histone deacetylases (HDACs), respectively [8]. Histone modifications can alter gene expression by acting in *cis*, in which the histone modification affects the DNA directly; for example, acetylation of lysine-rich N-termini of histone proteins, for example, can alter their electrostatic interaction with DNA and thereby the DNA's accessibility for transcription [40· 54· 77]. Histone modifications can also act in *trans*, in which changes to the histone tails act indirectly on the DNA; for example, acetylation of key lysine residues can create binding sites for the transcription machinery or other chromatin-modifying enzymes [8· 40· 54]. Histone methylation is generally associated with repressed chromatin while histone acetylation is associated with expressed chromatin; however, methylation and acetylation can exert different effects depending on sequence positions and combinations of the modified residues as well the histone being modified [40· 54· 77].

In the previously discussed study by Schober *et al.* where DNA methylation changes were seen at the IGF locus following controlled cortical impact, it was found that injury also promoted histone methylation and acetylation changes [86]. Controlled cortical impact increased H3K36 trimethylation at the promoter site 1 (P1) region of the IGF-1 gene, but decreased H3K36 trimethylation at the P2 region. H3K9 and H3K14 acetylation was increased in the P2 region of the IGF-1 gene, consistent with DNA methylation patterns and increased expression of the neuroprotective splice variant, IGF1B [86]. In contrast to this, at a more global level, Zhang *et al.* [108] using a fluid percussion model of TBI in rats, and Gao *et al.* [31] using a controlled cortical impact model of TBI in rats, have shown significantly less histone H3 acetylation in neuronal nuclei of surviving neurons. Similarly, Shein *et al.* have shown that histone H3 acetylation is significantly decreased in ipsilateral versus contralateral frontal cortical segments following a weight-drop contusion TBI in mice [87]. Yet other studies utilizing different animal models of TBI have failed to see changes in global histone acetylation in the brain [92· 105].

Taken together, these studies imply that while some specific gene regions may be acetylated (e.g. P2 region of the IGF-1 gene), on a genome-wide level, histones are generally deacetylated, raising the question of whether this general hypoacetylation following TBI is adaptive or maladaptive. In answer to this question, numerous studies have assessed the therapeutic efficacy of promoting histone acetylation using various classes of HDAC

inhibitors. In general, at therapeutic doses, most studies agree that post-injury administration of HDAC inhibitors can increase histone H3 and H4 acetylation, decrease blood brain barrier permeability, reduce neural damage, and improve cognitive and functional outcomes of TBI [25, 26, 31, 87, 92, 105].

MicroRNAs

In recent years, microRNAs (miRNAs) have been identified as relevant post-transcriptional regulators of various cellular functions in the brain under physiological and pathophysiological conditions, and their number is steadily increasing. miRNAs are short regulatory non-coding RNAs composed of 20–24 nucleotides, and are often located within introns [58]. Pre-miRNAs are processed into mature sequences, which target mRNAs in the cytosol. The miRNA binds to the 3'UTR region of the mRNA, which leads to degradation of the mRNA or direct inhibition of mRNA translation. A single miRNA can regulate a whole network of mRNAs [62]. Hence, targeting this family of small RNAs might help tackle the complex pathophysiological mechanisms, which occur during secondary brain injury. miRNAs have been found to be highly expressed in brain tissue and some seem to have brain specific functions [5, 9, 22].

Several studies during the last few years have investigated the role of miRNAs in different forms of CNS injury, including TBI, and it has been demonstrated that the expression levels of several miRNAs are significantly changed [6, 44, 59, 78–80, 95]. Downregulation of miR-23a and miR-27a was found in the injured cortex in the first 4 hours after TBI, and these changes coincided with increased expression of the proapoptotic Bcl-2 family members, NoxA, Puma and Bax [44].

Mitoeipigenetics

It is clear that epigenetic mechanisms such as DNA methylation, histone modifications and miRNA are regulated following TBI, though how these mechanisms impact outcome is less well studied: changes may be adaptive or maladaptive mechanisms, limit or exacerbate the symptoms, and promote or delay recovery. Given that diffuse white matter injury is associated with cytoskeletal perturbations and changes in mitochondrial integrity, movement and bioenergetics in axons [7, 32, 52, 60, 63, 73, 81], which may be some distance from the neuronal cell body and nucleus, it is reasonable to also consider epigenetic regulation of mitochondrial DNA in this review.

Similar to nucleic DNA, mitochondrial DNA (mtDNA) is regulated epigenetically. However, differing from the nuclear genome, mtDNA is circular, does not contain classical CpG islands, and is not associated with chromatin [17]. Rather, it is packaged into aggregates called nucleoids, which are coated with mitochondrial transcription factor A (TFAM, a HMG-like protein) that can physically impede accessibility to mtDNA by other proteins [56]. Methylation of mtDNA was first characterized in 1970's [69] and since then, 5-methylcytosine and 5-hydroxymethylcytosine have been observed in mammalian cells [88]. Although most of the mitochondrial proteins are encoded by the nuclear genome, 13 components of the oxidative phosphorylation cascade are encoded by the mitochondrial DNA (mtDNA) [3]. Directly relating mtDNA expression to bioenergetics, seven of these

products are subunits of complex I (NADH dehydrogenase), three are subunits of complex IV (cytochrome c oxidase), and two are subunits of complex V (ATP synthase) and cytochrome b (a subunit of complex III) [1, 27].

Of note, the first epigenetic enzyme characterized to methylate mtDNA was an isoform of DNMT called mitochondrial DNMT1 (mtDNMT1; [88]). mtDNMT1 was found to contain a mitochondrial targeting sequence allowing it to bind to the D-loop of the mitochondrial genome, which contains the promoter sites for both the light and heavy strand of mtDNA, suggesting it can modulate mitochondrial gene expression by altering transcriptional activity [88]. Indeed, overexpression of mitochondrial DNMT1 induces significant changes in mtDNA methylation levels [88]. Recent studies have also localized DNMT3A in the mitochondria of neurons [21, 101]. Importantly, the study by Wong *et al.* [101] revealed a clear correlation between DNMT3a localization and the presence of cytosine methylation in motor neuron mtDNA. Furthermore, decreased mitochondrial DNMT3A and aberrant mtDNA methylation has been observed in amyotrophic lateral sclerosis (ALS) [101].

Despite a rapidly growing field of study, there have yet to be any definitive reports on how epigenetic players such as DNMT1 and DNMT3A regulate organelle function. Since most of the mtDNA translate into products of the electron transport chain necessary to drive the production of ATP, it is feasible that epigenetic changes in the mitochondria could impact changes in bioenergetic output under TBI conditions. In this vein, different mtDNA haplogroups have been implicated in playing a role in TBI outcome in a number of studies. A population study conducted in England showed that mtDNA has a significant association with TBI outcomes, as certain haplogroups (K and T) have strong protective effect in TBI [15]. Another study reported that there is a strong correlation between mtDNA deletions in patients of acute brain injury [64]. The precise mechanisms of the link between mtDNA mutations and TBI outcome are currently unknown, but it is hypothesized that the diminished capacity for mtDNA to encode required elements of the electron transport chain contribute to worsened outcomes, and is supported by growing mechanistic insights in other neurodegenerative conditions as Parkinson's, Alzheimer's, Huntington's and motor neuron diseases [20].

Open questions and concluding remarks

As evident from the studies discussed in this review, the epigenome undergoes significant changes in the rodent brain following preclinical TBI, but we have only begun to scratch the surface in understanding what these complex epigenetic differences mean with respect to outcome and recovery. The general findings that there is global genomic hypomethylation and hypoacetylation following TBI offer little insight into the modulation of specific gene loci in specific cell types or brain regions [31, 108]. Moving forward, studies need to consider more comprehensive temporal, spatial and genome-wide approaches such as ChIP-Seq and bisulfite sequencing to properly understand the epigenetic landscape, determine what might be adaptive or maladaptive to recovery, and better tap into endogenous pathways for therapeutic intervention. For instance, differences in methylation of specific region of a gene, such as IGF-1, can yield alternative splicing that can impact neurological outcomes [16, 86]. Similarly, other epigenetic changes were found at the level of miRNAs where

dysregulation of specific transcripts are linked to mis-expression of various pro-apoptotic regulators such as Bcl-2 and cytochrome c [44].

As summarized in Table 1, therapeutic approaches aimed at the epigenetic level in TBI, where cognitive or functional recovery is measured as an output, have been scarce to date and have yielded mixed results. In one study, the HDAC inhibitor valproate was tested in rats subjected to TBI. Valproate increased histone acetylation and was associated with improved behavioral and cognition [26]. In contrast to this, a second study using fluoxetine also increased histone acetylation, but did not reveal any differences in functional assessments between treated TBI rats and controls [99]. In a third study, which used sodium butyrate as an HDAC inhibitor, TBI mice only showed improved outcomes when treatment was combined with behavioral therapy [25]. The differences in improvement between these studies likely reflect different TBI models, dosing strategies (3 hours post-injury for valproate, 3 days post-injury for fluoxetine, and 7 days for sodium butyrate), precise epigenetic targets of the differing agents, and differing environmental conditions (training versus non-training). These unclear outcomes demonstrate the desperate need for further studies with standardized models, treatments, and outcome measures to clarify the potential for epigenetic modulators as therapeutic interventions to improve recovery after TBI.

Mitochondria, which contain mtDNA that can also be regulated at an epigenetic level, add additional complexity to the understanding of the epigenetics of TBI. Although studies of mtDNA modification following TBI, and indeed other conditions of neurological injury, lag far behind other fields, findings that epigenetic regulators such as DNMT3A differ in mitochondrial expression and correlate with perturbed mtDNA methylation in an animal model of ALS [101], offer the possibility that changes might be seen following TBI. Since mitochondrial bioenergetics is known to be depressed following TBI [52], a looming question is whether or not TBI affects the regulation of mtDNA transcription, and if so, does it alter mitochondrial output? Furthermore, the fact that epigenetic regulators such as DNMT1 and DNMT3A are nuclear transcriptional products, and they carry out functions in both the nucleus and mitochondria implies a degree of nuclear-mitochondrial cross talk with respect to injury. Indeed, the genes of many enzymes crucial to the maintenance of mtDNA, such as mtDNA polymerase γ , helicase, primase and ligase, are encoded by nuclear genes [11, 35, 41, 55, 102]. Disturbance in mtDNA can result in neurological disorders include, but not limited to, Leigh syndrome [65], a progressive neurodegenerative condition (early onset), and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS; late onset) [34]. It is interesting to note that some of diseases show either loss of mtDNA, depletion of mtDNA, or accumulation of multiple mtDNA mutations/deletions.

It is likely that an epigenetic comparative study of both nuclear and mtDNA under basal and injury conditions will yield further significant insights to the nuclear-mitochondrial crosstalk at the epigenetic level. In addition to transcription and translation of proteins, it is tempting to envision that axonal transport of nuclear and mitochondrial epigenetic regulators such as DNMTs are being shuttled (anterograde and retrograde) along the microtubules for organelle crosstalk. This area is particularly important in the light that a diffused presence of amyloid-beta plaques, a hallmark pathological marker of Alzheimer's disease, have been identified in 30% of TBI patients [50], and that these plaques disrupt microtubule stability (among other

detrimental effects). Interestingly, tau oligomerization is found to accumulate in brains of post-TBI rats [38]. Such tauopathy can also be an additional malefactor of microtubule stability [98].

Beyond TBI-induced epigenetic changes, which may be adaptive or maladaptive to the recovering brain, studies in the normal brain have established roles for epigenetic modulators in neuroplasticity, learning and memory [100]. In fact, recent discoveries unravel the epigenetic modifications of histones and DNA can spearhead functional outcomes of neuronal circuitry and plasticity [100]. However, we have only begun to understand this relatively unexplored milieu, and the roles of such mechanisms in neuroplasticity following TBI have not been defined. Moreover, the possible epigenetic link between nuclear and mitochondria DNA can yield a novel and exciting field of study in a wide variety of neurological disease models. Given that cognitive impairment is one of the consequences of TBI, we stress that intervention by firstly understanding, and then modulating, the epigenetic landscape could offer tremendous promise for new therapeutic directions against such a neuropathological condition.

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Summary of epigenetic changes after TBI in animals and humans. In addition, some studies have further demonstrated the effects of epigenetic modifying drugs in post-TBI animals.

Table 1

TBI Model	Species	Epigenetic changes	Role	Epigenetic modifying drugs and outcomes	Reference
Air blast overpressure	Rat	Increased miR-let-7i	N/D	N/D	Balakathiresan N <i>et al.</i> 2012 [6]
		Increased neuronal DNA methylation	Decreased gene expression (sleep-wake regulators and TGF β)	N/D	Haghighi F <i>et al.</i> 2015 [37]
Controlled cortical impact	Rat	Decreased H3 acetylation Decreased H3 methylation	N/D	N/D	Gao WM <i>et al.</i> 2006 [31]
		Dynamic changes in miRNA levels	N/D	N/D	Redell JB <i>et al.</i> 2009 [78]
		Not compared	N/D	Valproate; histones (H3 and H4) acetylation; functional and cognitive improvement Suberoylanilide hydroxamic acid; histones (H3 and H4) acetylation; no functional and cognitive improvement	Dash PK <i>et al.</i> 2010 [26]
		No changes in histone acetylation	N/D	Fluoxetine; histone (H3) acetylation; no functional improvement	Wang Y <i>et al.</i> 2011 [99]
		Increased miR-21	Decreased expression of cell death protein 4	N/D	Redell JB <i>et al.</i> 2011 [80]
		Changes in DNA methylation, histone modifications	Increased IGF-1B	N/D	Schober ME <i>et al.</i> 2012 [86]
Fluid percussion	Mouse	Dynamic changes in miRNA levels	Genes involved in apoptosis, protein folding, and aerobic respiration	N/D	Hu Z <i>et al.</i> 2012 [44]
		N/D	N/D	Sodium butyrate; histones (H3 and H4) acetylation; cognitive improvement with concurrent behavioral training	Dash PK <i>et al.</i> 2009 [25]
	Rat	Decreased H3 acetylation	N/D	4-dimethylamino- <i>N</i> -(5-(2-mercaptoacetyl)amino)penyl benzamide (DMA-PB); increased histone (H3) acetylation, inhibition of microglia transformation into phagocytes.	Zhang B <i>et al.</i> 2008 [106]
		Dynamic changes in miRNA levels	N/D	N/D Hypothermia; inhibited TBI-induced upregulation of miRNAs	Lei P <i>et al.</i> 2009 [59] Truettner JS <i>et al.</i> 2011 [95]
Weight drop contusion	Rat	Decreased DNA methylation (microglia/macrophages)	Increased inflammatory activity	Dexamethasone; attenuated hypomethylation	Zhang ZY <i>et al.</i> 2007 [108]
Mild TBI	Human	Increased miR-16, miR-92a and miR-765	N/D	N/D	Redell JB <i>et al.</i> 2010 [79]