Neurotherapeutics (2013) 10:782–788
DOI 10.1007/s13311-013-0207-4

REVIEW

Epigenetics and the Modulation of Neuroinflammation

Gwenn A. Garden

Published online: 21 August 2013

Abstract Innate immune responses in the central nervous system (CNS) have key roles influencing both physiological and pathological processes. Microglia are innate immune effector cells that reside within the CNS. These inflammatory cells are constantly surveying their external environment and rapidly respond to a variety of molecules that signal changes in CNS homeostasis. In response to these signals, microglia influence neuronal connections, modulate the functions of other glia, and mediate inflammatory responses to disease or injury. In parallel with the regulation of inflammatory responses outside of the CNS, investigators have observed that microglia are capable of heterogeneous responses to exogenous and endogenous signals. While much of this molecular and morphological heterogeneity is regulated by gene transcription, there is ample evidence that microglial behavior is determined, in part, by epigenetic regulation. Recent work has demonstrated that processes involving DNA methylation, histone modification, and noncoding RNAs also have important roles in modulating neuroinflammation. Here I will review the evidence supporting a role for epigenetic regulation of neuroinflammation and describe how this might influence the outcome of several CNS disorders, including addiction, infection, multiple sclerosis, and stroke.

Keywords Microglia · DNA methylation · Histone acetylation · Histone deacetylase inhibitors · microRNA

Central Nervous System Innate Immune Effector Cells and Functional Differentiation

The overarching evolutionary purpose of inflammation biology is to restore physiological homeostasis following infection or injury. Thus, effective inflammatory responses must be transient, enabling a time-dependent response that is programmed to normalize once homeostasis is restored. Long-lived organisms have evolved to survive recurrent or chronic pathogen exposure through, in part, the development of the adaptive immune system and immunological memory. However, the innate immune system also requires careful feedback and time-dependent control to ensure that the host response to pathogens is appropriately tempered to eradicate the immediate threat without destroying the long-term ability of the organism to reproduce. This critical need for the innate immune system to respond to rapidly changing environmental cues makes the molecular regulation of inflammatory responses a likely target for epigenetic regulation. Inflammatory responses in the central nervous system (CNS) are mediated by a number of cell types, each of which may have unique mechanisms for epigenetic regulation. These include resident cells of myeloid origin (microglia), cells associated with the CNS vasculature, and inflammatory cells that traffic between the CNS and peripheral immune organs, as well as astrocytes derived from the neuroectoderm.

In the CNS, resident macrophages located within the parenchyma have been designated microglia. Based on the requirement for the PU.1(*Sfpi*1) transcription factor and the expression of many marker proteins in common with myeloid cells, it was hypothesized that microglia are derived from bone marrow. Bone marrow transplantation studies initially supported this hypothesis, as donor hematopoetic cells were able to migrate into the brain parenchyma and adopt typical microglia morphology [1]. However, it was later realized that microglia recruitment from transplanted hematopoetic cells in adult mice rarely occurs under basal conditions [2], suggesting that microglia are unlikely to be a default terminal differentiation pattern for circulating monocytes that enter the CNS. Recent studies have also demonstrated that the majority of microglia are yolk sac, rather than bone marrow-derived. They enter the brain very early in embryonic development through an obligate CSFR1 signaling mechanism common to several types of tissue macrophages [3, 4]. Once resident within the CNS, microglia appear to perform critical functions for the

G. A. Garden (✉)
Department of Neurology, University of Washington,
Seattle, WA 98195, USA
e-mail: gagarden@uw.edu

development of normal brain structure. Mice lacking CSFR1 have no microglia, structural brain abnormalities, and behavioral deficits [5]. Additional studies have also demonstrated that microglia participate in the process of synaptic pruning in response to sensory experience [6, 7].

Microglia were initially classified as quiescent or activated by morphological criteria. In the uninjured CNS, microglia have very small cell bodies and extensively ramified processes. *In vivo* imaging studies have revealed that in basal conditions, microglia are not actually quiescent. Their ramifications are continually in motion, appearing to actively survey their surrounding environment and rapidly changing morphology in response to neural injury [8]. Once exposed to signals indicating an alteration of homeostasis, microglia can respond with extensive functional heterogeneity. Microglia are capable of classical host defense responses that directly target pathogens such as the generation of reactive oxygen species and the release of molecular signals that recruit additional cellular participants to participate in the inflammatory response [9]. In addition, microglia can promote tissue homeostasis by phagocytic removal of pathogens and/or dead cells and the secretion of mediators that suppress inflammation, promote vascular expansion, and support neuronal survival [10, 11]. The molecular mechanisms that orchestrate these varied microglia responses or determine their temporal pattern of change have not been well delineated. My group, and others, have identified a number of key regulatory factors known to respond to inflammatory signals as influencing the pattern of subsequent microglia behavior [12–14]. Nevertheless, evidence exists to support the hypothesis that epigenetic factors also modulate microglia responses and may have important roles in mediating the response to chronic injury, infection, or inflammation in the CNS.

DNA Methylation as a Regulator of Microglia Behavior

Few studies have examined the effect of gene expression regulation by DNA methylation in microglia. Using a microglia-like cell line, investigators have reported that DNA methylation influences expression of several genes associated with the pathology of Alzheimer's disease [15, 16]. However, these studied do not clearly demonstrate that microglia behaviors are meaningfully altered *in vivo*. One very intriguing line of research demonstrating a role for methylation in the regulation of microglia behavior comes from the field of drug addition research. Exposing rats to morphine leads to increased pro-inflammatory cytokine and chemokine expression in the nucleus accumbens. Measures of subsequent addiction behavior are suppressed by promoting expression of the anti-inflammatory cytokine interleukin-10 (IL-10), which down-regulated the pro-inflammatory behavior elicited by morphine. Interventions that promote increased maternal care alter the methylation pattern of the *IL-10* gene, leading to increased IL-10 expression in the nucleus accumbens and a reduction in morphine-induced addiction behavior [17]. This study demonstrates a clear example of how an environmental exposure influences epigenetic change in CNS inflammatory cells, as well as how that change can have a long-term impact, increasing susceptibility for a psychiatric disorder. There are interesting parallels between this study and those performed on circulating inflammatory cells from patients with chronic depression. Compared with nondepressed controls, circulating inflammatory cells from patients with chronic depression demonstrated an altered pattern of DNA methylation, including changes in genes associated with a chronic inflammation, such as C-reactive protein and the pro-inflammatory cytokine IL-6 [18]. This study suggests that there is a relationship between epigenetic change in the regulation of inflammation and chronic depression; however, the causal direction of that relationship remains to be determined.

Histone Modification in Neuroinflammation

The epigenetic regulation of inflammation in a wide variety of settings has been demonstrated to involve changes in gene expression mediated by post-translational modification of histones [19]. Modifications can include acetylation, methylation, phosphorylation, ubiquitination, and citrullination. Owing to the availability of small molecules with therapeutic potential that specifically modulate histone acetylation, this is the most studied specific histone modification. Histones are acetylated by histone acetyl transferase enzymes, while histone deacetylases (HDACs) remove these modifications. Drugs with known anti-inflammatory and neuroprotective functions, such as valproic acid, have HDAC inhibitory activity [20, 21]. In addition, several specific small molecule HDAC inhibitors (HDACi) have been identified, some of which are currently in clinical use for cancer treatment. HDACi compounds have pro-apoptotic action on cancer cells, but—paradoxically—appear to be neuroprotective in a variety of settings [22, 23], as well as having potent anti-inflammatory effects [24, 25]. When HDACi compounds are tested *in vitro* or *in vivo*, they have also been demonstrated to modulate the neuroinflammatory response by preventing the transcriptional activity of known pro-inflammatory regulators [26, 27]. However, HDACs also acetylate lysine residues on a wide variety of molecules in addition to histones, including some key regulators of inflammation [19]. Therefore, the efficacy of HDACi at suppressing a tissue destructive pattern of inflammation may stem from mechanisms of action that do not involve epigenetic change.

In addition, HDACi studies *in vivo* may involve cell type-specific responses, influencing distinct patterns of gene expression in microglia and astrocytes [27]; thus, their precise

mechanisms of action in whole-animal studies are difficult to determine. For example, astrocytes are a key component of the inflammatory response in the CNS parenchyma. Under basal conditions, astrocytes secrete factors that elicit microglia quiescence, such as transforming growth factor beta isoforms, suppressing microglia pro-inflammatory responses [28]. In pro-inflammatory conditions, HDAC activity increases in astrocytes, leading to loss of antioxidant defenses. HDACi can prevent astrocyte dysfunction initiated by pro-inflammatory microglia [29]. HDACi also promote astrocyte-mediated release of neurotrophic factors [30], suggesting a parallel with microglia where pro-inflammatory signals decrease histone acetylation leading to tissue destructive actions, while inhibiting HDACs yields gene expression patterns associated with tissue repair.

Perhaps owing to, in part, this convergent pattern of behavior in response to HDACi in astrocytes and microglia, this class of compound has great potential utility in modulating neuroinflammation to prevent CNS injury. Nevertheless, the actions of HDACi in CNS injury are difficult to study because the compounds are hypothesized to have both neuroprotective and anti-inflammatory effects. Preventing neuronal injury may decrease neuroinflammation, while ameliorating the inflammatory response may also lesson neuronal injury. Therefore, experiments aimed at examining the mechanisms of action of HDACi should evaluate biomarkers for both activities in addition to examining the overarching impact of these compounds on the restoration of normal neurological function.

HDACi were initially developed for their anti-tumor properties, but have since been identified to have neuroprotective action in a number of settings. When HDACi were tested on *in vivo* models of neural injury, such as experimental stroke, they were demonstrated to possess anti-inflammatory, as well as neuroprotective, actions [31], suggesting important therapeutic potential for preventing morbidity and mortality from CNS injury. One CNS disorder identified as potentially benefitting from HDACi was multiple sclerosis. This autoimmune disorder is associated with inflammatory demyelination and subsequent neurodegeneration. Thus, it was hypothesized that the ability of HDACi to both suppress inflammation and promote neuronal survival would have therapeutic benefit [32, 33]. Using the experimental autoimmune encephalitis (EAE) model of multiple sclerosis, it was observed that HDACi ameliorates inflammation and improves pathology of axons and myelin [34], suggesting potential clinical utility of this class of drug for a CNS disorder, and highlighting that inflammatory regulation is influenced by HDACi.

Another example of potential clinical utility for HDACi in modulation of neuroinflammation is in the area of traumatic brain injury (TBI). Tissue destructive neuroinflammation is one factor believed to exacerbate the long-term consequences of TBI (loss of function, as well as post-traumatic epilepsy). In a rat TBI model, treatment with the HDACi 4-dimethylamino-N-[5-(2-mercaptoacetylamino)pentyl]benzamide prevented signs of both neuroinflammation and neurodegeneration 24 hours after injury [35]. It was also observed that treatment with HDACi following TBI led to increased p53 and caspase activation, specifically in microglia [36], suggesting that neuroprotection from HDACi may involve suppression of the inflammatory response by promoting apoptosis of inflammatory cells when they are induced to proliferate by pro-inflammatory signals. A similar finding was observed when HDACi treatment was given in a rodent model of spinal cord injury [37].

Another example has come from the study of Huntington's disease (HD). Studies in yeast demonstrated the mutant huntingtin (Htt) promotes the kynurenine pathway. In mice, mutant Htt influences the kynurenine pathway in microglia, leading to increased production of neurotoxic metabolites, and this effect of mutant Htt involves HDAC activity [38]. Treatment of an HD mouse model with HDACi normalized activity of the kynurenine pathway in microglia both *in vitro* and *in vivo* [38], suggesting that one mechanism of the neuroprotective action of HDACi in HD models involves modulation of microglia gene expression.

Taken together, this group of studies suggests that modulating the CNS inflammatory response through pharmacological blockade of HDAC activity may have an important role in future therapeutic strategies for a variety of CNS disorders. However, given the potentially important role for HDACs in the regulation of gene expression in organs outside of the CNS, the therapeutic potential of this class of compounds for chronic disorders remains a question. Additional studies are needed to determine which specific histone modifications or protein acetylations should be modulated in order to consider epigenetic regulation of CNS inflammation a viable therapeutic target.

Regulation of Neuroinflammation by Non-coding RNA

A third mechanism of epigenetic regulation of gene expression is through non-coding RNAs. RNA molecules that do not code for protein are prevalent within total RNA samples [39], and modulate gene expression and protein translation through a number of mechanisms. The most well studied form of non-coding RNA is microRNA (miRNA). miRNAs employ complementary binding to the 3' untranslated region of mRNAs and suppress expression of their target mRNAs both by preventing translation and promoting mRNA degradation [40]. Each individual miRNA has multiple targets, thus having the capacity to concurrently modulate a large number of proteins. Owing to this broad action, it has been hypothesized that individual miRNAs may be key modulators of whole patterns of cellular behavior. For example, miRNA profiling

of specific CNS cell types revealed that each of the major cell types within the brain has a restricted pattern of miRNA expression, with some miRNAs promoting neuronal differentiation, while others clearly support glial differentiation patterns [41]. This profiling study identified a miRNA expression profile that differentiates microglial cells from neurons and neuroglia (Table 1). This unique expression profile may represent the distinct origin and function of microglia cells within the CNS.

Some miRNAs have been identified as promoting pro-inflammatory behaviors, while others are associated with deactivation of the inflammatory response. The regulation of innate immune responses by miRNAs is an exciting topic of research, but it remains unclear whether miRNA-based regulation of peripheral macrophage/monocyte behavior will be recapitulated in microglia. Some well-studied miRNA modulators of inflammation have been evaluated in cultured microglia and have generally been observed to recapitulate the functions observed in macrophages. miRNA-155 promotes pro-inflammatory functional differentiation in lymphocytes and myeloid cells in response to signaling by cytokines or activation of Toll-like receptors. In microglial cells, miR-155 is up-regulated by Toll-like receptor activation and represses expression of the suppressor of cytokine signaling-1 protein, enabling the subsequent up-regulation of pro-inflammatory cytokine secretion [42]. Interestingly, the gene for miR-155 is located on human chromosome 21, suggesting that trisomy 21 patients might be at risk for increased neuroinflammation. Brains from patients with trisomy 21 do demonstrate increased miR-155 and microglia activation, perhaps contributing to the increased risk of Alzheimer's disease in this population [43]. MiR-146a is another miRNA with a well-described role in modulation of the inflammatory response. Pro-inflammatory signaling leads to up-regulation of MiR-146a expression, but this miRNA subsequently targets pro-inflammatory molecules for suppression, thereby serving as a negative feedback loop on the activation of pro-inflammatory behavior. Pro-inflammatory signaling leads to increased expression of miR-146a in microglia and subsequent decreased expression of molecules needed to maintain the pro-inflammatory behavior [44].

Table 1 microRNA (miRNA) species enriched or depleted>5-fold in microglia compared to other central nervous system cell types [41]

Enriched miRNAs	Diminished miRNAs
miR-126, miR-126*, miR-141, miR-142-3p, miR-142-5p, miR-146a, miR-150, miR-200c, miR-223	miR-9, miR-9*, miR-124, miR-127, miR-129, miR-129*, miR-135a, miR-135b, miR-136, miR-137, miR-153, miR-204, miR-325-3p, miR-335, miR-384-5p

In the normal adult brain, microglia appear to have a molecular phenotype suggesting inflammatory quiescence, expressing low levels of major histocompatibility complex class II and co-stimulatory molecules [45]. After exposure to an inflammatory stimulus, microglia initiate a similar pattern of new gene expression compared with peripheral macrophages, but the size of theses changes is quantitatively reduced [45]. As such, the inflammatory activation of microglia is a likely potential target for epigenetic regulation by miRNAs, as each miRNA can suppress expression of a large number of target genes without necessarily changing the overall pattern of gene expression. Several miRNA regulators of inflammatory cell behavior have been identified, and some have been demonstrated to play critical roles in the pathogenesis of CNS diseases. One example is miRNA-124, a miRNA that suppresses the expression of transcriptional regulators of macrophage activation. In response to the EAE model of multiple sclerosis, miR-124 is down-regulated in microglia, while exogenous delivery of miR-124 lead to marked reduction in the severity of EAE [46].

Another example of an important miRNA-based modulation of neuroinflammation that influences disease pathogenesis has been reported in a study aimed at elucidating the mechanisms of neuronal injury in HIV-associated neurocognitive disorders (HAND). One model of HAND pathogenesis involves cellular dysfunction and microglia activation caused by secreted HIV proteins, including Tat. When human microglia cells are exposed to Tat, they increase expression of miR-32, which represses tumor necrosis factor-receptor-associated factor 3 and leads to the subsequent up-regulation of interferon response factor-3 (IRF-3) and IRF-6 [47]. Increased IRF-3 can, in turn, further exacerbate neuroinflammation by promoting the expression of miR-155 [48], suggesting a mechanism by which Tat exposure may further amplify chronic inflammation that contributes to eventual neurological dysfunction in HAND. It has also been reported that infection of microglia by HIV leads to increased expression of miR-146a, which subsequently suppress pro-inflammatory behavior and the release of CCL8/monocyte chemoattractant protein 2 (MCP-2) [49]. As MCP-2 can serve to block cellular entry by HIV, the role of miR-146a may have duel effect in perpetuating HAND by both suppressing endogenous antiviral proteins and decreasing the release of MCP-2. A similar role for miR-146a has been proposed for prion disease, where increased expression of miR-146a is observed in microglia [50].

The neuroinflammatory response to ischemia has also been reported to involve miRNAs. Microglia exposed to oxygen glucose deprivation (OGD) release inflammatory mediators, such as tumor necrosis factor alpha (TNF) and Fas ligand (FasL), which are toxic to surrounding neurons and may exacerbate neural injury following stroke. The expression of TNF and FasL following OGD are influenced

by miR-181c and miR-21, respectively, and over-expression of these miRNAs in microglia exposed to OGD suppresses release of TNF and FasL, as well as protecting neurons co-cultured with OGD treated microglia [51, 52]. miR-424 is another miRNA with an established role in the regulation of macrophage inflammatory response by suppressing expression of proteins involved in cell cycle progression. In stroke patients, as well as the middle cerebral artery occlusion (MCAO) model of stroke, miR-424 is decreased, suggesting that reduced expression of this miRNA may enable the pro-inflammatory response to proceed [53]. When expression of miR-424 was induced by lentiviral gene transfer in the MCAO model infarct volume, brain edema, markers of neuroinflammation, and neuronal apoptosis were all significantly reduced [53]. These findings suggest that modulation of miRNAs may be a means of modulating the inflammatory response to reduce neurodegeneration after an ischemic insult.

Another example of a proposed miRNA-based therapeutic intervention in stroke involves the Let7f miRNA, which suppresses mRNA for the neurotrophic factor insulin-like growth factor 1 (IGF-1). IGF-1 is protective in a rat MCAO model of stroke, specifically in middle-aged females with age-related declines in IGF-1. Delivery of a stabilized anti-miRNA targeting Let7f also decreased infarct volume and improved behavioral outcomes after MCAO in middle-aged female rats [54]. Interestingly, the majority of Let7f was detected in microglia cells, and alterations in IGF-1 secretion were only observed when microglia isolated from the ischemic side of the brain were exposed to anti-Let7f [54]. These findings suggest the possibility that the effect of anti-Let7f may modulate the inflammatory response by promoting a pattern of functional differentiation similar to alternative activation in macrophages, rather than just specifically targeting the expression of IGF-1. As would be predicted by a broader effect on microglia activation state of anti-Let7f, this study also demonstrated increased expression of brain-derived neurotrophic factor and prostaglandin E2 synthase [54].

In summary, these studies all demonstrate that CNS inflammatory responses are strongly influenced by alterations in the expression of a number of miRNA species. These miRNAs subsequently influence the functional heterogeneity of cells participating in the inflammatory response to disease, infection, or injury through an epigenetic mechanism.

Conclusions and Future Questions

As discussed above, several studies demonstrate that the molecular regulation of neuroinflammation is strongly influenced by epigenetic mechanisms. Perhaps the most exciting conclusion to be drawn from studies performed to date is that modulation of epigenetic factors can influence not only the neuroinflammatory features in CNS disease and injury, but can also affect the functional and anatomical outcome in animal models of these disorders. These studies have provided important support for the hypothesis that modulation of neuroinflammatory responses aimed at suppressing the tissue destructive actions and promoting tissue repair functions can yield important benefit in a variety of CNS disorders for which current therapeutic options have limited efficacy. Additionally, as the modification of histones can be targeted by pharmacological compounds with HDACi activity (some of which are already in use for cancer treatment) it is possible that drugs that promote histone acetylation will rapidly move into clinical trials for acute CNS injury. Given the potential for deleterious off-target effects from HDACi with broad activity, it will likely require much more extensive knowledge of the precise molecular targets for acetylation needed to modulate the pathogenesis of chronic neurodegenerative disorders like HD and Alzheimer's disease. Targeted pharmacological manipulation of miRNAs also holds future promise. However, much more study is needed to identify miRNAs with the potential to specifically affect the CNS inflammatory response with limited off-target effect.

Required Author Forms Disclosure forms provided by the authors are available with the online version of this article.

Disclosures None.

References

1. Ono K, Takii T, Onozaki K, Ikawa M, Okabe M, Sawada M. Migration of exogenous immature hematopoietic cells into adult mouse brain parenchyma under GFP-expressing bone marrow chimera. Biochem Biophys Res Commun 1999;262:610–614.
2. Ajami B, Bennett JL, Krieger C, Tetzlaff W, Rossi FM. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. Nat Neurosci 2007;10:1538–1543.
3. Schulz C, Gomez Perdiguero E, Chorro L, et al. A lineage of myeloid cells independent of Myb and hematopoietic stem cells. Science 2012;336:86–90.
4. Ginhoux F, Greter M, Leboeuf M, et al. Fate mapping analysis reveals that adult microglia derive from primitive macrophages. Science 2010;330:841–845.
5. Erblich B, Zhu L, Etgen AM, Dobrenis K, Pollard JW. Absence of colony stimulation factor-1 receptor results in loss of microglia, disrupted brain development and olfactory deficits. PLoS One 2011;6:e26317.
6. Schafer DP, Lehrman EK, Kautzman AG, et al. Microglia sculpt postnatal neural circuits in an activity and complement-dependent manner. Neuron 2012;74:691–705.
7. Paolicelli RC, Bolasco G, Pagani F, et al. Synaptic pruning by microglia is necessary for normal brain development. Science 2011; 333:1456–1458.

8. Davalos D, Grutzendler J, Yang G, et al. ATP mediates rapid microglial response to local brain injury in vivo. Nat Neurosci 2005;8:752–758.
9. Garden GA, Moller T. Microglia biology in health and disease. J Neuroimmune Pharmacol 2006;1:127–137.
10. Boche D, Perry VH, Nicoll JA. Review: activation patterns of microglia and their identification in the human brain. Neuropathol Appl Neurobiol 2012;39:3–18.
11. Colton CA. Heterogeneity of microglial activation in the innate immune response in the brain. J Neuroimmune Pharmacol 2009; 4:399–418.
12. Jayadev S, Nesser NK, Hopkins S, et al. Transcription factor p53 influences microglial activation phenotype. Glia 2011;59:1402–1413.
13. Jayadev S, Case A, Eastman AJ, et al. Presenilin 2 is the predominant gamma-secretase in microglia and modulates cytokine release. PLoS One 2011;5:e15743.
14. Saijo K, Winner B, Carson CT, et al. A Nurr1/CoREST pathway in microglia and astrocytes protects dopaminergic neurons from inflammation-induced death. Cell 2009;137:47–59.
15. Byun CJ, Seo J, Jo SA, et al. DNA methylation of the 5'-untranslated region at +298 and +351 represses BACE1 expression in mouse BV-2 microglial cells. Biochem Biophys Res Commun 2011;417:387–392.
16. Lin HC, Hsieh HM, Chen YH, Hu ML. S-Adenosylhomocysteine increases beta-amyloid formation in BV-2 microglial cells by increased expressions of beta-amyloid precursor protein and presenilin 1 and by hypomethylation of these gene promoters. Neurotoxicology 2009;30:622–627.
17. Schwarz JM, Hutchinson MR, Bilbo SD. Early-life experience decreases drug-induced reinstatement of morphine CPP in adulthood via microglial-specific epigenetic programming of anti-inflammatory IL-10 expression. J Neurosci 2011;31:17835–17847.
18. Uddin M, Koenen KC, Aiello AE, Wildman DE, de los Santos R, Galea S. Epigenetic and inflammatory marker profiles associated with depression in a community-based epidemiologic sample. Psychol Med 2010;41:997–1007.
19. Halili MA, Andrews MR, Sweet MJ, Fairlie DP. Histone deacetylase inhibitors in inflammatory disease. Curr Top Med Chem 2009;9:309–319.
20. Chen PS, Wang CC, Bortner CD, et al. Valproic acid and other histone deacetylase inhibitors induce microglial apoptosis and attenuate lipopolysaccharide-induced dopaminergic neurotoxicity. Neuroscience 2007;149:203–212.
21. Xuan A, Long D, Li J, et al. Neuroprotective effects of valproic acid following transient global ischemia in rats. Life Sci 2012;90:463–468.
22. Leng Y, Liang MH, Ren M, Marinova Z, Leeds P, Chuang DM. Synergistic neuroprotective effects of lithium and valproic acid or other histone deacetylase inhibitors in neurons: roles of glycogen synthase kinase-3 inhibition. J Neurosci 2008;28:2576–2588.
23. Langley B, D'Annibale MA, Suh K, et al. Pulse inhibition of histone deacetylases induces complete resistance to oxidative death in cortical neurons without toxicity and reveals a role for cytoplasmic p21(waf1/cip1) in cell cycle-independent neuroprotection. J Neurosci 2008;28:163–176.
24. Licciardi PV, Ververis K, Tang ML, El-Osta A, Karagiannis TC. Immunomodulatory effects of histone deacetylase inhibitors. Curr Mol Med 2012;13:640–647.
25. Shuttleworth SJ, Bailey SG, Townsend PA. Histone Deacetylase inhibitors: new promise in the treatment of immune and inflammatory diseases. Curr Drug Targets 2010;11:1430–1438.
26. Faraco G, Pittelli M, Cavone L, et al. Histone deacetylase (HDAC) inhibitors reduce the glial inflammatory response in vitro and in vivo. Neurobiol Dis 2009;36:269–279.
27. Suh HS, Choi S, Khattar P, Choi N, Lee SC. Histone deacetylase inhibitors suppress the expression of inflammatory and innate immune response genes in human microglia and astrocytes. J Neuroimmune Pharmacol 2010;5:521–532.
28. Pratt BM, McPherson JM. TGF-beta in the central nervous system: potential roles in ischemic injury and neurodegenerative diseases. Cytokine Growth Factor Rev 1997;8:267–292.
29. Correa F, Mallard C, Nilsson M, Sandberg M. Activated microglia decrease histone acetylation and Nrf2-inducible anti-oxidant defence in astrocytes: restoring effects of inhibitors of HDACs, p38 MAPK and GSK3beta. Neurobiol Dis 2011;44:142–151.
30. Chen SH, Wu HM, Ossola B, et al. Suberoylanilide hydroxamic acid, a histone deacetylase inhibitor, protects dopaminergic neurons from neurotoxin-induced damage. Br J Pharmacol 2011;165:494–505.
31. Kim HJ, Rowe M, Ren M, Hong JS, Chen PS, Chuang DM. Histone deacetylase inhibitors exhibit anti-inflammatory and neuroprotective effects in a rat permanent ischemic model of stroke: multiple mechanisms of action. J Pharmacol Exp Ther 2007;321:892–901.
32. Faraco G, Cavone L, Chiarugi A. The therapeutic potential of HDAC inhibitors in the treatment of multiple sclerosis. Mol Med 2011;17: 442–447.
33. Gray SG, Dangond F. Rationale for the use of histone deacetylase inhibitors as a dual therapeutic modality in multiple sclerosis. Epigenetics 2006;1:67–75.
34. Camelo S, Iglesias AH, Hwang D, et al. Transcriptional therapy with the histone deacetylase inhibitor trichostatin A ameliorates experimental autoimmune encephalomyelitis. J Neuroimmunol 2005; 164:10–21.
35. Zhang B, West EJ, Van KC, et al. HDAC inhibitor increases histone H3 acetylation and reduces microglia inflammatory response following traumatic brain injury in rats. Brain Res 2008;1226:181–191.
36. Shein NA, Grigoriadis N, Alexandrovich AG, et al. Histone deacetylase inhibitor ITF2357 is neuroprotective, improves functional recovery, and induces glial apoptosis following experimental traumatic brain injury. FASEB J 2009;23:4266–4275.
37. Lu WH, Wang CY, Chen PS, et al. Valproic acid attenuates microgliosis in injured spinal cord and purinergic P2X4 receptor expression in activated microglia. J Neurosci Res 2013;91:694–705.
38. Giorgini F, Moller T, Kwan W, et al. Histone deacetylase inhibition modulates kynurenine pathway activation in yeast, microglia, and mice expressing a mutant huntingtin fragment. J Biol Chem 2008; 283:7390–7400.
39. Paschoal AR, Maracaja-Coutinho V, Setubal JC, Simoes ZL, Verjovski-Almeida S, Durham AM. Non-coding transcription characterization and annotation: a guide and web resource for non-coding RNA databases. RNA Biol 2012;9:274–282.
40. Lee S, Vasudevan S. Post-transcriptional stimulation of gene expression by microRNAs. Adv Exp Med Biol 2012;768:97–126.
41. Jovicic A, Roshan R, Moisoi N, et al. Comprehensive expression analyses of neural cell-type-specific miRNAs identify new determinants of the specification and maintenance of neuronal phenotypes. J Neurosci 2013;33:5127–5137.
42. Cardoso AL, Guedes JR, Pereira de Almeida L, Pedroso de Lima MC. miR-155 modulates microglia-mediated immune response by down-regulating SOCS-1 and promoting cytokine and nitric oxide production. Immunology 2011;135:73–88.
43. Li YY, Alexandrov PN, Pogue AI, Zhao Y, Bhattacharjee S, Lukiw WJ. miRNA-155 upregulation and complement factor H deficits in Down's syndrome. Neuroreport 2011;23:168–173.
44. Li YY, Cui JG, Dua P, Pogue AI, Bhattacharjee S, Lukiw WJ. Differential expression of miRNA-146a-regulated inflammatory genes in human primary neural, astroglial and microglial cells. Neurosci Lett 2011;499:109–113.
45. Ponomarev ED, Veremeyko T, Weiner HL. MicroRNAs are universal regulators of differentiation, activation, and polarization of microglia

and macrophages in normal and diseased CNS. Glia 2013;61:91–103.
46. Ponomarev ED, Veremeyko T, Barteneva N, Krichevsky AM, Weiner HL. MicroRNA-124 promotes microglia quiescence and suppresses EAE by deactivating macrophages via the C/EBP-alpha-PU.1 pathway. Nat Med 2010;17:64–70.
47. Mishra R, Chhatbar C, Singh SK. HIV-1 Tat C-mediated regulation of tumor necrosis factor receptor-associated factor-3 by microRNA 32 in human microglia. J Neuroinflammation 2012;9:131.
48. Tarassishin L, Loudig O, Bauman A, Shafit-Zagardo B, Suh HS, Lee SC. Interferon regulatory factor 3 inhibits astrocyte inflammatory gene expression through suppression of the proinflammatory miR-155 and miR-155*. Glia 2011;59:1911–1922.
49. Rom S, Rom I, Passiatore G, et al. CCL8/MCP-2 is a target for mir-146a in HIV-1-infected human microglial cells. FASEB J 2010; 24:2292–2300.
50. Saba R, Gushue S, Huzarewich RL, et al. MicroRNA 146a (miR-146a) is over-expressed during prion disease and modulates the innate immune response and the microglial activation state. PLoS One 2012;7:e30832.
51. Zhang L, Dong LY, Li YJ, Hong Z, Wei WS. miR-21 represses FasL in microglia and protects against microglia-mediated neuronal cell death following hypoxia/ischemia. Glia 2012;60:1888–1895.
52. Zhang L, Dong LY, Li YJ, Hong Z, Wei WS. The microRNA miR-181c controls microglia-mediated neuronal apoptosis by suppressing tumor necrosis factor. J Neuroinflammation 2012;9:211.
53. Zhao H, Wang J, Gao L, et al. MiRNA-424 protects against permanent focal cerebral ischemia injury in mice involving suppressing microglia activation. Stroke 2013;44:1706–1713.
54. Selvamani A, Sathyan P, Miranda RC, Sohrabji F. An antagomir to microRNA Let7f promotes neuroprotection in an ischemic stroke model. PLoS One 2012;7:e32662.