Chapter 13

Neuroinflammation on the Epigenetics of Neural Stem Cells

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1. Introduction

Under physiological conditions, neuronal stem cells (NSCs) can undergo both self-renewal and differentiation stages. The formation of new neurons, neurogenesis, is a vital process by which the brain maintains its lifelong plasticity in response to extrinsic and intrinsic changes. However, the exact mechanisms that regulate NSC self-renewal and differentiation are largely unknown. NSCs become stimulated after neuronal injury and can migrate at pathological sites (Nakatomi et al., 2002; Russo et al., 2011) that dictate the potential of NSCs therapeutic use in pathological conditions of the central nervous system. In this chapter, we describe the effect of neuroinflammation in NSCs and discuss whether the inflammatory mediators can epigenetically affect the capacity of NSCs and alter their proliferation and differentiation ability. The mechanism by which the inflammatory environment influences the NSC niche and thus, alters the self-renewal, survival, migration, and differentiation of the NSCs is currently unknown (Martino and Pluchino, 2006). Several studies have focused the effects of inflammation on the regenerative capacity of NSCs subjected to microglial activation after an acute injury or after LPS treatment. Overall, the connection between brain inflammation and NSC neurogenesis and the role of the niche in the modulation of neuronal differentiation under alternative conditions are under intense investigation.

To gain further insight into these phenomena, we describe epigenetic mechanisms, including DNA methylation and histone modification in NSCs inflammation. DNA methylation and histone modification are known to play significant roles in the modulation of stem cell proliferation and differentiation (Li and Zhao, 2008). Regarding DNA methylation, methylated CpG-binding protein (MBD) deficiency results the suppression of NSCs differentiation. Therefore, to identify the downstream target genes of MBDs has potential in NSCs differentiation study. Histone modifications are another important epigenetic mark. There are many

types of post-translational modifications of the residues at histone tails, including methylation of lysines and arginines, acetylation, phosphorylation, ubiquitination, SUMOylation, and ADP-ribosylation. Among the histone modifications, histone H3 lysine (K) methylation is a central epigenetic modification with both activating and repressive roles in eukaryotic chromatin (Reinberg et al., 2004).

Next, we will focus on epigenetic involvement in neurodegenerative diseases and NSCs. Actually, inflammatory stimuli induce beneficial effects (e.g., phagocytosis of debris and apoptotic cells), and inflammation is linked to tissue repair processes, uncontrolled inflammation may result in production of neurotoxic factors that amplify underlying disease states and pathogenesis of Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and a growing number of other nervous system pathologies (Glass et al., 2010). Here, endogenous NSCs cannot fully compensate the neuronal loss in such neurodegenerative diseases. The possible reasons include the lack of trophic support and inhibitory signals within the brain microenvironment (Croft and Przyborski, 2009), indicative of oxidative stress (Kelly et al., 2011) and age-related neuroinflammation. In summary, the recent development of stem cells technology open new areas of research aimed at stimulating neuronal regeneration in the brain during aging, neuroinflammation and neurodegenerative diseases (Russo et al., 2011). Here, we overview the therapeutic approach of NSC and how these stem cells are responsible for brain homeostasis, induction of neurogenesis in several diseased states. Finally, this chapter indicates the possibility of combination therapy of epigenetic drug with NSC transplantation in these neurodegenerative diseases.

2. Epigenetics and neuroinflammation

Alterations in cell signaling by environmental changes can remodel epigenetic marks (Borrelli et al., 2008; Weaver et al., 2007). Epigenetics thus presents potential explanations for sustained changes in transcriptional activity associated with cell differentiation, learning and memory, age-related neurodegeneration and effects of early experience, repeated drug exposure, chronic stress, and environmental toxins. The implicit hypothesis is that environmental signals alter chromatin modifications, which then serve as the mechanism for the transcriptional 'plasticity' that mediates sustained variation in neural function (Meaney and Ferguson-Smith, 2010). Although most extensively studied in embryonic stem cells, such 'bivalent' domains, which are also found in the adult brain (Sanz et al., 2008), suggest a developmentally 'poised' state awaiting environmental direction. Indeed, such states may mark the potential for plasticity. The same epigenetic mark can recruit effectors that activate as well as others that repress transcription. We describe the detail epigenetic changes in NSC later in this chapter. We summarize the recent evidence that physiological and environmental signals influence adaptive transcriptional responses in neurons through the epigenetic modification of chromatin. We highlight to the regulation of histone modifications and DNA methylation in response to neuroinflammation and related signaling. In addition, mechanisms that induce chromatin modifications in association with multiprotein complexes on neuronal gene promoters are mentioned.

3. NSC and inflammation

To maintain brain homeostasis, NSCs are highly controlled under physiological conditions in which the stem cell niche is vital for the NSC self-renewal, proliferation, differentiation, and migration. NSCs become activated after neuronal injury and migrate to the site of injury, indicating that some regulators at the injury site can guide the migration of precursor cells. Damaged neurons can be repaired by the activation of endogenous neuronal stem cells, which migrate to regions of the brain injury, differentiate into neuronal cells, and integrate into neuronal circuits (Belmadani et al., 2006; Russo et al., 2011) The mechanism by which the inflammatory environment influences the NSC niche and thus, alters the self-renewal, survival, migration, and differentiation of the NSCs is currently unknown (Martino and Pluchino, 2006). Alterations of NSC functions either pro-neurogenic or anti-neurogenic in inflammation may depend on the NSC niche and activation of brain microglial cells. It is reported that activated microglia in inflammatory conditions can inhibit neurogenesis (Butovsky et al., 2006). On the contrary, activated microglia also showed helpful for neurogenesis (Hanisch and Kettenmann, 2007). Inflammatory cytokines and nitric oxide (NO) released by microglial cells can inhibit the adult neurogenesis. Activation of microglia with LPS results the production of inflammatory mediators in vitro, including TNF-α and IL-6, that inhibit the generation of neurons from NSCs (Monje et al., 2003). However, modification of microglial status by other cytokines, such as IL-4 or low dose interferon-γ (IFN-γ) changes their phenotype to strongly promote neurogenesis (Butovsky et al., 2006). However, the positive effects are at least partly dependent on microglia production of insulin-like growth factor-1 (IGF-1), a potent proneurogenic growth factor. Though controversial, this raises the possibility that some types of controlled inflammation may be exploited in CNS regeneration or in combating neurological diseases that have pronounced chronic proinflammatory components (Rolls et al., 2009)

Several studies have focused the effects of inflammation on the regenerative capacity of NSCs subjected to microglial activation after an acute injury or after LPS treatment. It is reported that TLR4 is expressed by NSCs, and LPS suppresses the proliferation of NSCs under culture conditions via an NF-κB-dependent mechanism (Monje et al., 2003; Rolls et al., 2007). In addition, TLR4 can directly modulate the self-renewal and cell-fate decision of neuronal progenitor cells (Rolls et al., 2007). Overall, the effects of proinflammatory signaling on NSCs go beyond simple changes in the abundance of new neurons (Carpentier and Palmer, 2009). It is shown that the neurons generated during the period of inflammation are morphologically normal, with normal cell body location, polarity, and branching, yet they display an accentuated inhibitory or excitatory responses in immature versus mature neurons, respectively (Jakubs et al., 2008). So, the functions of new neurons are severely affected by immune signaling. Moreover, the connection between brain inflammation and NSC neurogenesis and the role of the niche in the modulation of neuronal differentiation under alternative conditions are under intense investigation.

4. Epigenetic significance in NSC-inflammation

Epigenetic refers to any heritable influence (in the progeny of cells or individuals) on chromosome or gene function that is not accompanied by a change in DNA sequence (Yoder et al., 1997). It includes processes such as DNA methylation, histone modification and noncoding RNA expression. Appropriate gene function either activation or repression at inflammatory stages of NSC progression could be achieved by such epigenetic regulation. Here, we cover recent reports involving the role of epigenetic mechanisms in NSC-inflammation and its fate on NSC mechanisms. One of the important epigenetic mechanisms, DNA methylation in the genome is established by a family of DNA methyltransferases (DNMTs). Maintenance of methylation patterns is achieved by a function of DNMT1 during DNA replication, while de novo methylation is primarily catalyzed by DNMT3a and DNMT3b. DNA methylation is responsible for the regulation of gene expression, where two mechanisms are involved. First, methylation of CpG dinucleotides affects DNA structure and can directly interfere with the binding of TFs to their target sequences(Takizawa et al., 2001); second, a more pervasive effect, methyl-CpG-binding domain (MBD)-containing protein family members can bind to genes with methylated CpG dinucleotides, thereby suppressing the genes' expression (Nan et al., 1997) Though, DNA methylation is actively involved in the acquisition of multipotentiality in NSC from early-, mid- to late-gestation. Here, we mainly focus on two well-studied pathways that act synergistically to promote astrocytic differentiation of NSC are those activated by the interleukin-6 (IL-6) family of cytokines such as leukemia inhibitory factor (LIF), ciliary neurotrophic factor (CNTF) and cardiotrophin-1 (CT-1) and bone morphogenetic protein (BMP) signaling (Juliandi et al., 2010). In early- and mid-gestational NSCs, astrocytic gene promoters such as glial fibrillary acidic protein (GFAP) are hypermethylated, a status that impedes binding of the STAT3-p300/CBP-SMADs complex to its target sequence and thus prevents these NSCs from differentiating into astrocytes even when the cells are stimulated by astrocyte-inducing cytokines (Takizawa et al., 2001). These IL-6 family cytokines have been shown to be expressed in NSCs and neurons in the fetal mouse brain (Barnabe-Heider et al., 2005); but how DNA methylation of IL-6 does affect of NSC differentiation in inflammation is not disclosed. On the contrary, the STAT3 binding site-containing GFAP promoter in NSCs at late gestation is barely methylated, so that upon LIF stimulation these NSCs can differentiate into astrocytes (Takizawa et al., 2001). Overall, the genome-wide DNA methylation status of NSCs in well-defined inflammatory conditions may give us possible clue of gene specific methylation status of NSC whether DNA methylation can play an important role in defining the NSC fate from neurogenesis to astrocytogenesis in inflammatory conditions. Notch signaling is a conserved pathway from insects to mammals, which contributes to cell-to-cell communication (Louvi and Artavanis-Tsakonas, 2006) and controls cell fate determination in the CNS (Lundkvist and Lendahl, 2001). Upon Notch activation by its ligand, the Notch intracellular domain (NICD) is released from the plasma membrane and is translocated into the nucleus, where it converts a particular repressor complex into an activator complex (Nakayama et al., 2008). It is confirmed that Notch ligands are indeed expressed in neuronally committed NPCs and young neurons, and that these ligands activate Notch signaling in the residual NSCs. Further, forced expression of NICD in midgestational NSCs induced the

upregulation of nuclear factor 1A (NF1A), which in turn accelerated demethylation of astrocytic gene promoters by preventing DNMT1 from binding to them and thus allowed precocious astrocytic differentiation in response to LIF stimulation (Namihira et al., 2009).

It has shown that methyl binding domain (MBD) proteins expressed predominantly in neurons, and not in astrocytes or oligodendrocytes, in the CNS (Kishi and Macklis, 2004); may regulate in NSC differentiation. It was found that exon1 of GFAP are hypermethylated in all neural cell types and that only in neurons, methyl-CpG-binding protein 2 (MeCP2), a member of the MBD family, is highly expressed and binds to this methylated exon1 region (Setoguchi et al., 2006) that is linked to block the astrocyte differentiation. Indeed, ectopic expression of MeCP2 directs NSCs to become neurons and inhibits astrocytic differentiation, even in the presence of astrocyte-inducing cytokines such as LIF and BMP2 (Tsujimura et al., 2009). MBD1-deficient NSCs generate fewer neurons than do wild type NSCs, suggesting an important role for MBD1 in neuronal fate specification (Zhao et al., 2003).

Histone proteins within the chromosome play a significant role in chromatin structure, gene transcription and epigenetic information. Multiple modifications decorate each histone tail within the nucleosome, and some amino acids on the histone tail can be modified in several different ways. Covalent modifications of histone taile include methylation, acetylation, phosphorylation, ubiquitylation, sumoylation, glycosylation, biotinylation, carbonylation and adenosine diphosphate (ADP)-ribosylation (Strahl and Allis, 2000). Among these, modifications by histone acetylation and methylation are the most common. Acetylation and deacetylation of lysine residue in histone tails is mediated by histone acetyl transferases (HATs) and histone deacetylases (HDACs), respectively (Hsieh and Gage, 2005). Histone acetylation by HATs is responsible for open chromatin (euchromatin) formation that leads to transcriptional activation. Conversely, HDACs result decrease of histone acetylation and formation of condensed chromatin (heterochromatin) that causes transcriptional silencing. Adult hippocampal-derived NSCs differentiate predominantly into neurons, at the expense of astrocytes and oligodendrocytes, when treated by the antiepileptic and HDAC inhibitor valproic acid (VPA) in vitro, even in conditions that favor glia-specific differentiation (Hsieh et al., 2004). VPA-mediated HDAC inhibition upregulates the neuron-specific gene NeuroD, a neurogenic basic helix-loop-helix transcription factor (TF), is resulting in the induction and suppression, respectively, of neuronal and glial differentiation. In the developing rat brain and in cultured E14 NSCs, VPA treatment has also been shown to promote neurogenesis by activating the Ras-ERK pathway (Jung et al., 2008).

Histone methylation is involved in the regulation of a variety of nuclear processes dedicated to the maintenance of active and silent states of gene expression, which is essential for cellular regulation, homeostasis and fate determination (Cloos et al., 2008). There are five lysine residues in the histone N termini that are prominently methylated. H3K4 and H3K36 methylation primarily transduce activating functions, whereas H3K9, H3K27, and H4K20 methylation is mainly associated with repressed chromatin. Histone lysine methylationcan result in mono-, di-, or trimethyl states and each distinct methylation state confers different biological read-outs. Histone lysine trimethyl states, particularly those with repressive functions, appear relatively robust because they are stably propagated during several cell divisions (Lachner et

al., 2004). Among the histone modifications, histone H3 lysine (K) methylation is a central epigenetic modification with both activating and repressive roles in eukaryotic chromatin (Reinberg et al., 2004). JmjC domain proteins demethylate histone lysine and arginine residues in an oxidative reaction that requires Fe (II) and α-ketoglutarate as cofactors. Depending on their target specificity, JmjC domain proteins promote transcriptional repression or activation, thereby impacting important processes such as hormone response, stem cell renewal, germ cell development, and cellular proliferation and differentiation (Beyer et al., 2008). Interestingly, a range of JmjC proteins is induced in different cancers and has been linked to cell proliferation (Cloos et al., 2006) and the suppression of senescence (Pfau et al., 2008). Members of the JMJD2 family that target H3K9me3/me2 and H3K36me3/me2 are highly expressed in prostate cancer (Wissmann et al., 2007).

Recently, we reported the effect of lipopolysaccharides (LPS) on NSCs epigenetics, where we used an immortalized neuroectodermal stem cell line, NE-4C. The NE-4C cell line was cloned from the anterior brain vesicles of E9 mouse embryos lacking functional p53 (Livingstone et al., 1992). Non-induced NE-4C cells grow as homogeneous, epithelial-like populations, and in response to all-trans retinoic acid (RA) treatment, they differentiate into neurons on a highly reproducible schedule (Jelitai et al., 2004). We found that histone demethylase, Jmjd2b is functional in long-term LPS treatment and regulates the histone demethylation of the promoters of its target genes that may be crucial in multiple signaling pathways and biological processes in murine NSCs (NE-4C cells). MetaCore pathway analysis revealed the gene networks and canonical pathways affected in Jmjd2b-attenuated NE-4C cells that involved neurophysiological processes (receptor-mediated axon growth repulsion, GABA-A receptor life cycle), the Notch1-mediated pathway for NF-κB activity modulation, and TGF-β-dependent induction. Several extrinsic factors affect the histone methylation status of NSCs. In the postnatal mouse brain, MLL1 is required for neurogenesis and its deficiency in NSCs in the subventricular zone (SVZ) leads to a glial lineage preference. One of the key downstream regulators of SVZ neurogenesis, Dlx2, is not expressed in MLL1-deficient NSCs. This is due to a change in histone methylation of Dlx2, from a single high level of H3K4 trimethylation (H3K4me3) to a bivalent poised state marked by both activating H3K4me3 and repressive H3K27me3 (Lim et al., 2009).

We found that Jmjd2b is functional in long-term LPS treatment and regulates the histone demethylation of the promoters of its target genes that may be crucial in multiple signaling pathways and biological processes in NE-4C cells. Jmjd2b is a newly identified member of the histone demethylase Jmjd2 family that is characterized by the catalytic Jumonji C (JmjC) domain. Jmjd2b specifically targets the trimethylated lysine 9 of histone H3 (H3K9) for demethylation at pericentric heterochromatin and euchromatin (Fodor et al., 2006). It is reported that JMJD2B is critical to breast cancer cell survival under conditions of normoxia and hypoxia, which occurs partially via the regulation of cell cycle progression, is highly expressed in ERα-positive primary breast cancers, and is an adverse prognostic factor in hypoxic breast cancers (Yang et al., 2010). In this study, MetaCore pathway analysis was used to reveal the gene networks and canonical pathways affected in Jmjd2b-kd cells. Among the network, generation of neurons, neurogenesis, cell differentiation, and cellular developmental

processes were most significantly affected in Jmjd2b-attenuated NE-4C cells. The significantly downregulated genes were clustered in different networks and canonical pathways. We found that Jmjd2b-kd NE-4C cells downregulated various key genes involved in neurophysiological processes (receptor-mediated axon growth repulsion, GABA-A receptor life cycle), the Notch1-mediated pathway for NF-κB activity modulation, and TGF-β-dependent induction. Jmjd2b encodes a histone demethylase that has been recently shown to be a HIF-1α target gene (Yang et al., 2009). Jmjd2b attenuation significantly inhibited p65, iNOS, Bcl2 and TGF-β expression in JMJD3-kd NE-4C cells. A GeneGo analysis of Jmjd2b-kd NE-4C cells revealed that Jmjd2b attenuation affected the generation of neurons, neurogenesis, system development, cell differentiation and cellular development processes. Several genes involved in the receptor-mediated axon growth repulsion (semaphorin 3a, pleiotrpphin-OSF1, ephrin A receptor 2), the GABA-A receptor life cycle (GABA-A receptor beta 2), the NOTCH1-mediated pathway for NF-κB activity modulation (c-Rel, Jagged 1, p65/p52) and the TGF-β-dependent induction (TGF-β2, Jagged1, N-cadherin, Lef1) were directly or indirectly affected by Jmjd2b attenuation. We predict that Jmjd2b recruitment may be necessary for the expression of regulated genes from several pathways that are crucial for various neurological functions. These results suggest that LPS has an inflammatory effect on NE-4C cells via epigenetic modulation.

It has also been reported that the mRNA expression of NeuroD, a neural progenitor cell marker, was significantly decreased in the hippocampus of aged mice compared with that in young mice. In light of previous results, we examined the presence of H3K9me3 at the NeuroD promoter but did not observe a reduction of the H3K9me3 level in Jmjd2b-kd NE-4C cells. We predicted that other histone modifications might be involved at the promoter site of NeuroD for its expression. However, the functions of most histone demethylases, including Jmjd2b, are not clear under inflammatory conditions, and the mechanism by which Jmjd2b epigenetically regulates gene expression in NSC inflammation has not been well shown. Therefore, the clarification of the function of Jmjd2b may help to identify novel therapeutic targets for brain inflammation.

5. Epigenetic regulations of proinflammatory cytokines in NSC

Cytokines are the secreted molecules that mediate communication between immune cells and between immune system and host. Cytokines encompass a broad class of signaling molecules that have the potential to influence an immense variety of signals that regulate NSC function, including growth factor production, electrical activity, synaptic function, and axonal path finding (Carpentier and Palmer, 2009). We will focus our discussion on the epigenetic regulations of inflammatory cytokines in NSC. Though, several recent reports shown that important cytokines include TNF-α, IL-6, and IL-1β have prominent inhibitory effect on adult neurogenesis in vivo. TNF-α can induce apoptosis in NSCs or newborn neurons via TNFR1. TNFR1 signaling, but not that of TNFR2, has been demonstrated to inhibit neurogenesis in the normal hippocampus (Iosif et al., 2006). In addition, neurogenesis is severely affected by another strong inflammatory mediator, NO. It has been reported that the SVZ cell proliferation rate is significantly increased after the inhibition of neuronal NOS activity (Sun et al., 2005). Notably, the

pathological concentration of NO has a skewing effect on NSC differentiation when the pro-astroglial fate is very dominant (Covacu et al., 2006). At present, not many studies have been reported regarding the epigenetic involvement for cytokine regulations in NSC; recently, we reported LPS could affect NSC in vitro via epigenetic regulation (Das et al., 2012). The in vitro treatment of NE-4C cells with LPS (1 μg/ml for 96 h) significantly increased Jmjd2b expression and decreased the levels of H3K9me3. It has been reported that IL-1β suppresses the proliferation of hippocampal progenitor cells (Koo and Duman, 2008).The decreased proliferation of neural stem cells is responsible for decreased neural differentiation, and increased proliferation could correspond to the promotion of neurogenesis. We predicted that H3K9me3 is involved in Jmjd2b-attenuated NE-4C cells. A ChIP analysis showed that Jmjd2b-attenuated samples experienced an increase in the H3K9me3 on inflammatory signaling-mediated genes. An induced presence of H3K9me3 has been observed at the promoters of the Notch1, IL-1β, and IL-2 genes in Jmjd2b-kd NE-4C cells, suggesting that Jmjd2b can fine-tune the local chromatin state to enhance the transcription of these genes (Das et al., 2012).

6. Potential of NSC in neurodegenerative diseases

Neurogenesis by endogenous NSC cannot fully overcome the neuronal loss observed in neurodegenerative diseases. One reason for this limited response is the lack of trophic support and inhibitory signals within the brain microenvironment (Croft and Przyborski, 2009), indicative of oxidative stress and age-related neuroinflammation. These observations stimulated a search for agents that could increase neurogenesis and enhance neuroprotection (Russo et al., 2011). Now we will discuss the various neurodegenerative diseases including Alzheimer'sdisease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), epilepsy, and stroke in inflammatory contexts. Each of the neurodegenerative diseases considered here is distinguished by a disease-specific mechanism for induction of inflammatory responses. The distinct pathways for production of inducers of inflammation—such as Ab, a-synuclein, mutant SOD1, and myelin peptide mimetic—and the specific anatomical locations at which these processes occur are likely determinants of the specific pathologicial features of each disease. In particular, TLRs and other pattern recognition receptors expressed on microglia and astrocytes are likely to play significant roles in initiating inflammatory responses. Later the downstream signal transduction pathways like NF-κB and AP-1 appear to play general roles in mediating the production of amplifiers and effector molecules, such as cytokines (e.g., TNF-α, IL-1β, and IL-6), ROS, and NO which involving in neurotoxicity for all of the neurodegenerative diseases (Glass et al., 2010).

Now we will focus on epigenetic involvement for such neurodegenerative diseases. Genes that are epigenetically regulated in Alzheimer's disease are *S100A2* (a member of the S100 family of calcium-binding proteins) and *SORBS3* (a sorbin and SH3 domain containing the cell-adhesionProtein) that display significant different level of DNA methylation (Siegmund et al., 2007). S100A2 has been previously identified as a metastatic inductor in non-small-cell lung cancer (Bulk et al., 2009), but its role in Alzheimer's disease pathogenesis remains unknown.

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Most importantly, S100B, another member of the S100 family, which acts as a neurotrophic and pro-survival neuronal factor, might have a role in Alzheimer's disease pathogenesis and how does the exogenous and endogenous NSC express and epigenetically regulate such neurotrophic factors is still unknown. Among other epigenetic regulations in the pathogenesis of PD; DNA hypomethylation of TNF-α can directly lead to specific vulnerability of the substantianigra could be the direct consequence of PD (Pieper et al., 2008) and that may potentiate why the cytokine mediate inflammation is one of the major causes for PD. It is also reported that TNF-α overexpression induces apoptosis in neuronal cells and TNF-α levels are high in the CSF of patients with Parkinson's disease (Mogi et al., 1996). Multiple sclerosis is an inflammatory chronic disease characterized by a demyelinating process, which is followed by neurodegeneration. Although little is known about the epigenetics of this disease, some evidence suggests hypomethylation was proven at the promoter region of *PADl2* (peptidyl arginine deiminase, type II), also found to be overexpressed in multiple sclerosis. PADl2 catalyzes the citrullination of myelin basic protein that can change the properties of myelin (Mastronardi et al., 2007; Urdinguio et al., 2009). Epilepsy is described as a common chronic neurological disorder characterized by recurrent spontaneous seizures. Sporadic epilepsy can arise as a result of traumatic brain injury, stroke, abnormalities in brain wiring, toxic-metabolic etiologies, inflammation, autoimmunity, or an imbalance in the ratio of inhibitory to excitatory synaptic transmission (Hwang et al, 2012; Berg et al, 2010). Spontaneous seizures activate REST and promote deacetylation of core histone protein H4 (a mark of gene repression) at the RE1 site of the gria2 promoter (gene encoding the AMPAR subunit GluA2) recruits mSin3A and CoREST, HDACs-1/2, G9a and MeCP2, while promoting an increase in acetylation of H4 (a mark of open chromatin) at the promoter of brain-derived neurotrophic factor BDNF (Tsankova et al, 2004). Although, GluA2 expression was decreased, leading to an increase in GluA2-lacking, Ca2+-permeable AMPARs at CA3 synapses and neuronal death in CA3. Alterations of these proteins contribute to the pathophysiology of recurrent seizures. In epileptic adult rats transplanted fetal NSC (E14 rat) cells differentiated into neurons (13%, mostly GABAergic) and astrocytes (57%) and showed a reduction of motor seizure by 43% and severe convulsive seizure by 90% (Waldau et al., 2010). But how does the epigenetic regulators in exogenous NSC play crucial role in epilepsy yet to disclose. Ischemic insults also trigger activation of REST in mature hippocampal neurons destined to die and that the increase in REST correlates with a decrease in histone acetylation and gene silencing of GluA2. This is significant in that the GluA2 subunit prevents Ca2+ influx via AMPA receptors (AMPARs), is essential to synapatogenesis, long lasting forms of synaptic plasticity and neuronal death (Hwang et al., 2012; Liu and Zukin, 2007). Since, REST is a master transcriptional regulator of neuronal genes in pluripotent stem cells and neural progenitors and that loss of REST during the late stages of neural differentiation by ubiquitin based proteosomal degradation is required for acquisition of the neural phenotype (Hwang et al., 2012). The more study needs to answer how does REST perform at transplanted NSC in stroke model and whether other synaptic proteins correlate with REST for neuronal death in a clinically relevant ischemic stroke model.

Finally, more research will be required to understand the epigenetic mechanisms that underlie the neuroprotective roles of NSC in neurodegenerative diseases.

7. Conclusion

Due to self-renewal ability and differentiation to various neural cell types, NSC has great potential for clinical treatment of neurological diseases and dysfunctions. This regenerative capacity of NSC hold a great promise to open new areas of research aimed at stimulating neuronal regeneration in the brain during aging, neuroinflammation and neurodegenerative diseases. Epigenetic regulation along with other mechanisms can control these properties of NSCs. However, our knowledge about the precise mechanisms that control NSC function in neuroinflammation is still in its infancy and many avenues remain to be explored. The acute innate proinflammatorysignaling cascade strongly suppresses the production and retentionof new neurons in the adult brain. Here, the related immune signaling and epigenetic role might involve that must be addressed. We are just at the beginning of understanding the field. There are not reproducible comprehensive profiles of the DNA methylomes and histone modifications of NSCs in proper inflammatory stages that could generate some biomarkers to test in disease-associated conditions. Although more neurodevelopmental diseases caused by mutations in epigenetic genes are being identified, we still do not understand how the disturbance of DNA methylation and histone modification would directly affect NSC fate except the regulation of some neurotrophic factors. Moreover, a clear epigenetic interpretation that control the stimulation of neurogenesis during neuroinflammation, and the integration of NSC in diseased brain could assist to develop novel therapeutic approaches with a potential application in neuroinflammatory diseases.

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