8. Neurodegenerative disorders and inflammation

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Abstract. Neurodegenerative diseases are characterized by the loss of specific neuronal populations. Epidemiological studies and pathological analyses have demonstrated the existence of a link between mutations in specific genes and heritable forms of neurodegenerative diseases. Although some of these mutations can be found in higher frequency among certain ethnic populations, together they account for only a small percentage of all cases. Therefore, at the present it is well accepted that the causes of idiopathic or non-familial forms of neurodegenerative diseases are multifactorial, including genetic predisposition, epigenetic factors, age, and even environmental factors.

Although the key molecular and cellular events underlying the development of neurodegenerative diseases such as Alzheimer's, Parkinson's, Huntington's and multiple sclerosis, are clearly different, a common feature between them is neuroinflammation. In this context, the central nervous system has long been considered to be an immune-privileged site because of the presence of the blood–brain barrier and the lack of a lymphatic system, still it is now well established that it is fully capable of mounting an inflammatory response. Invading
pathogens, trauma, stroke, intraneural as well as extracellular fibrillary material can trigger local invasion of circulating immune cells, production of reactive oxygen and nitrogen species, as well as the activation of the brain resident macrophages known as microglia. Inflammation in the central nervous system has been appropriately described as a two-edged sword; in acute situations inflammatory mechanisms limit injury and promote healing; however, in a chronic situation neuroinflammation can seriously damage viable host tissue. Current studies support the notion that neuroinflammation promotes or facilitates neurodegeneration; therefore, early intervention with anti-inflammatory therapies in populations identified to be at risk due to genetic mutations may represent a valuable tool. We present recent data regarding non-genetic mechanisms that regulate the development of neurological disorders including Huntington’s disease, multiple sclerosis, Parkinson’s disease and Alzheimer’s disease.

Inflammatory response in the central nervous system

The central nervous system (CNS) has been considered an immunologically privileged site because the blood–brain barrier (BBB), under normal physiological conditions, does not allow the passage of inflammatory cells and mediators from the bloodstream into the brain parenchyma. However, during an inflammatory process high concentrations of pro-inflammatory cytokines\(^1\), such as interleukin-1 beta (IL-1\(\beta\)) and tumor necrosis factor alpha (TNF-\(\alpha\)), alter the permeability of the BBB allowing the passage of immunocompetent cells to the brain (1, 2) (Table 1). Accordingly, there are several studies that have reported that the inflammatory response in the brain is associated with the development and progression of many neurological diseases such as stroke, multiple sclerosis, Alzheimer’s disease, Huntington’s disease, Parkinson’s disease, among others. However, little is known about the molecular mechanisms that allow the establishment of chronic inflammation in the brain and how inflammation may contribute to the development of such pathologies.

In the CNS, immune surveillance is conducted primarily by microglial cells, which constitute the 10% of all glial cells\(^3\). Microglia are derived from myeloid precursor cells and in response to an injurious stimulus, such as infection, they increase their phagocytic capacity and the expression of molecules of the major histocompatibility complex\(^3\) class I (MHCI) and MHCII, and also produce cytokines, chemokines, reactive oxygen species (ROS) and reactive nitrogen species (RNS) (3-9). In addition to microglia,

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\(^1\)Cytokines: are signaling molecules that induce activation, proliferation and cell differentiation, chemotaxis and apoptosis via specific membrane receptors.

\(^2\)Glial cells: The support cells associated with neurons (astrocytes, oligodendrocytes and microglia in the central nervous system; Schwann cells in the peripheral nerves; satellite cells in ganglia).

\(^3\)MHC: Large transmembrane, polymorphic glycoproteins which control the immune response to specific antigens.
macrophages associated to the **meninges**, **perivascular space**\(^4\), the **choroid plexus**\(^5\) and to the circum ventricular organs, possess higher phagocytic capacity and present higher expression levels of MHCII compared to microglia. Interestingly, both astrocytes and neurons are also capable of producing inflammatory mediators (10, 11). Astrocytes are the most numerous glial cells in the brain, are responsible of promoting neuronal survival, and also form an important part of the BBB. Although generally not considered immunocompetent cells, astrocytes express pattern recognition receptors (PRRs) that are able to distinguish between bacterial and viral stimuli by differentially producing cytokines and chemokines (12, 13). In addition to MHCII, astrocytes express co-stimulatory molecules at low levels upon exposure to interferon-γ (IFN-γ) (14). These observations suggest that astrocytes may play a role in the **secondary response**\(^6\) (15). Furthermore, neurons also express different PRRs (TLRs -2, -3,-4, -8 and NALP1) and are capable of initiating proinflammatory responses against pathogens such as virus (16-18) (**Figure 1**).

In response to injury or infection, cytokines and chemokines including IL-1β, TNF-α, IL-6, IL-8 and MCP-1 (monocyte chemo attractant protein1) produced in the CNS induce the migration and diapedesis of neutrophils, macrophages, dendritic cells (DCs) and lymphocytes. Peripheral immune cell migration through the BBB involves the transmigration across the vascular endothelium that is connected by complex tight junctions and the progression through the astrocyte network into the brain parenchyma where they exert their action (19). DCs are present in the perivascular spaces, the meninges and the choroid plexus in healthy individuals. However, during infection or injury DC numbers drastically increase and they migrate to the parenchyma. In an infection, antigen presentation occurs initially in perivascular spaces. Both perivascular macrophages and DCs are responsible of **naïve T cells**\(^7\) activation by the presentation of antigens. T cells activation leads to their differentiation into a subset of effect or cells (**Th1**\(^8\), **Th2**\(^9\), **Th17**\(^10\) and **Treg**\(^11\)) influenced by the predominant cytokine microenvironment. Neuroinflammation may be triggered by immunological challenges (bacterial or viral infections), environmental toxins (pesticides, particulate matter), neuronal injury (brain

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\(^4\)**Meninges**: The external covering of the brain; includes the pia, arachnoid and dura matter.

**Perivascular space**: Subpial compartments surrounding blood vessels throughout the brain.

\(^5\)**Choroid plexus**: Specialized epithelium in the ventricular system that produces the cerebrospinal fluid.

\(^6\)**Secondary response**: is the activation of primed T cells resulting from antigen presentation by non-professional antigen-presenting cells.

\(^7\)**Naïve T cells**: are lymphocytes that have never encountered their specific antigen.

\(^8\)**Th1**: subset of helper T cells that secrete IFN-γ leading to macrophage activation.

\(^9\)**Th2**: subset of helper T cells that secrete IL-4 and IL-5, which activate B cells and IL-10, which inhibits macrophage activation.

\(^10\)**Th17**: subset of T helper cells that produce IL-17. Excessive amounts of these cells are thought to play a key role in autoimmune diseases.

\(^11\)**Treg**: can actively suppress antigen specific responses following rechallenge with antigen.
Table 1. Inflammatory mediators in the central nervous system.

<table>
<thead>
<tr>
<th>MEDIATOR</th>
<th>ORIGIN</th>
<th>FUNCTION</th>
<th>REFERENCES</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1β</td>
<td>Microglia, astrocytes, neurons</td>
<td>Vasodilation, recruitment of neutrophils and mononuclear cells</td>
<td>(1, 5)</td>
</tr>
<tr>
<td>IL-6</td>
<td>Microglia, astrocytes</td>
<td>Fever, production of prostaglandins, apoptosis</td>
<td>(5)</td>
</tr>
<tr>
<td>IL-18</td>
<td>Microglia, astrocytes</td>
<td>Activation of microglia, production of IFN-γ</td>
<td>(39)</td>
</tr>
<tr>
<td>TNF-α</td>
<td>Microglia, astrocytes</td>
<td>Vasodilation, recruitment of monocytes, production of chemokines, apoptosis</td>
<td>(5, 6)</td>
</tr>
<tr>
<td>IL-8</td>
<td>Microglia</td>
<td>Recruitment of neutrophils and monocytes</td>
<td>(6)</td>
</tr>
<tr>
<td>RANTES</td>
<td>Astrocytes</td>
<td>Neuronal migration, differentiation and proliferation of astrocytes</td>
<td>(40)</td>
</tr>
<tr>
<td>MCP-1</td>
<td>Microglia, astrocytes</td>
<td>Recruitment of mononuclear cells</td>
<td>(6)</td>
</tr>
<tr>
<td>MIP-1α</td>
<td>Microglia</td>
<td>Recruitment of neutrophils</td>
<td>(6)</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>Astrocytes</td>
<td>Production of nitric oxide and chemokines, activation of macrophages and natural killer cells</td>
<td>(7)</td>
</tr>
<tr>
<td>IL-17</td>
<td>Microglia</td>
<td>Production of proinflammatory cytokines, chemokines and prostaglandins</td>
<td>(8)</td>
</tr>
<tr>
<td>ROS</td>
<td>Microglia, astrocytes, neurons</td>
<td>Structural damage, recruitment of leukocytes, activation of microglia and redox signaling</td>
<td>(9)</td>
</tr>
<tr>
<td>NO</td>
<td>Microglia, astrocytes, neurons</td>
<td>Structural damage, recruitment of leukocytes, activation of microglia</td>
<td>(3)</td>
</tr>
</tbody>
</table>
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trauma or stroke), or even by chronic inflammatory syndromes (rheumatoid arthritis, arthrosclerosis, Crohn's disease and MS) (20-27). Depending on the context, duration, and type of the inflammatory response, inflammation may be detrimental or beneficial to the individual.

Previous studies provide a link between aberrant gene expression patterns with neuro inflammation and neurodegeneration (28, 29). Interestingly, in addition to genetic predisposition other nongenetic gene-regulatory factors including miRNA-mediated post-transcriptional gene regulation (BOX 1) and epigenetic mechanisms (e.g. DNA methylation and histone modifications, BOX 2) have been recently suggested to influence both susceptibility and severity of specific neurological diseases (30). miRNAs are endogenous small non-coding RNAs (sncRNAs) of 18-22 base pairs (bp) that act to repress the expression of their target genes at the post-transcriptional level, either by mRNA degradation or by translational inhibition. In the CNS of numerous organisms the expression of different miRNAs has been reported to be crucial for its correct development and function. miRNAs also participate during the

Figure 1. Inflammation in the central nervous system. Inflammation in the CNS is initiated in response to damage (physical, chemical or biological), which induces the production of cytokines and chemokines such as IL-1β, TNF-α and IL-8. These inflammatory mediators alter the permeability of the BBB, allowing the passage of immune cells and inflammatory mediators from the bloodstream into the brain parenchyma. Additionally, infection in peripheral organs induces chronic inflammation and the release of inflammatory mediators into the bloodstream, which activates immune cells that can travel through the bloodstream to the CNS, contributing to the inflammatory process.
immune system development and immune response, consequently miRNAs dysregulation results in autoimmunity. In fact, miRNAs are important for the correct differentiation and function of immune cells (e.g. B cells, T cells and dendritic cells) (31-33). Many recent studies provide a link between miRNA function and neurodegeneration (34-36). Conditional loss of miRNA expression in the brain leads to neurodegeneration in several animal models (37). Evidences from patient studies indicate that miRNA dysregulation could contribute to neurodegenerative disorders (38). The translation of proteins previously implicated in familial forms of disease seems to be under control of miRNAs, and changes in miRNAs might explain how these proteins become affected in sporadic neurodegeneration. Thus, miRNAs are rapidly moving to center stage as key regulators of neuronal development and function, as well as important contributors to neurodegeneration.

Correct epigenetic regulation has also been shown to be important in the development and function of the CNS, immune system and inflammation. Additionally, recent studies have shown that dysregulation of these mechanisms can lead to different developmental neuropathologies and neurodegenerative diseases (BOX 2). However, evidence linking epigenetic mechanisms with neurodegeneration and inflammation are still scarce. Thus, better understanding of the nongenetic mechanisms might shed light on the neuropathogenesis and also on potential approaches for managing or even suppressing the diseases. In this chapter we summarize recent advances in our understanding of the participation of these mechanisms in regulating immune responses and in the development of different neurodegenerative diseases including Huntington’s disease, multiple sclerosis, Parkinson’s disease and Alzheimer’s disease. We also discuss the potential of miRNAs and epigenetic marks as diagnostic and prognosis indicators of disease type, severity and as novel therapeutic targets for specific neurological disorders.

**Huntington’s disease**

Huntington’s disease (HD) is an inherited genetic disorder characterized by a progressive degeneration of the striatum12 and cerebral cortex13. The symptoms include motor, cognitive and psychiatric disorders. G. Huntington initially described HD in 1872. HD can occur at any age, however, the first symptoms usually appear between 30-40 years of age. The mutation responsible for this disease is an expansion of the trinucleotide CAG repeat in

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12**Striatum**: subcortical part of the forebrain. It is the major input station of the basal ganglia system. The striatum, in turn gets input from the cerebral cortex.

13**Cerebral cortex**: The superficial gray matter of the cerebral hemispheres. The cerebral cortex plays a role in memory, language and consciousness.
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exon 1 of the gene encoding the huntingtin (Htt) protein that is translated as a polyglutamine repeat. Mutant forms of huntingtin (mHtt) with 36 or more repetitions of the trinucleotide accumulate in the nucleus and cytoplasm of neurons and glia, inducing cell death (41). Additionally, mHtt processing by proteolytic enzymes, such as metalloproteases, generates fragments that cannot be eliminated, thus contributing to the formation of aggregates and enhancing neurotoxicity (42). In the brain, huntingtin is normally found in high concentrations and has a role in transcription, transport, and in the secretion of trophic factors such as the brain-derived neurotrophic factor (BDNF) (43). The lack of this important factor may explain some of the clinical features of HD, as BDNF deficiency is characterized by memory loss and motor dysfunction, which are alterations also observed in HD (44, 45).

Although a direct relationship between inflammation and the development of HD has not been established, there are reports suggesting that an inflammatory process could favor the development of the disease. Recently, Khoshnan et al. demonstrated that mHtt activates IKK (IκB kinase), promoting the expression of genes regulated by NF-κB (nuclear factor kappa B) (46). Accordingly, high concentrations of IL-6, IL-8 and TNF-α in plasma and cerebrospinal fluid14 (CSF) have been reported in HD patients. Furthermore, Reijonen et al. found a correlation between increased proinflammatory cytokines and the progression of the disease (47). However, the role of NF-κB in the development of HD is controversial. The activity of NF-κB decreases with increasing mHtt protein aggregates as a result of a decreased concentration of the p65 subunit of NF-κB (48). Additionally, mHtt inhibits the expression of RANTES (regulated upon activation, normal T-cell expressed and secreted), whose expression is regulated by NF-κB. RANTES is a chemokine important for neuronal migration and astrocyte proliferation. Therefore, the unavailability of RANTES may contribute to neuronal dysfunction in HD (40). Taken together, these evidences suggest the involvement of NF-κB in an inflammatory process in HD, which may depend on the stage of the disease.

The activation of caspase-1 is one of the first events observed in the pathogenesis of the disease in a murine model of HD, which correlates with an increase in the concentration of RIP2 (receptor interacting protein-2) and a decrease in the inhibitory molecule COP (caspase recruitment domain only protein) (53). Moreover, several studies have demonstrated an increased production of ROS and IL-1β in HD patients (54-56). These results suggest the possible participation of the inflammasome15 as a triggering mechanism of the inflammatory process that could favor the pathogenesis of the disease.

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14Cerebrospinal fluid: fluid produced in the choroid plexus of the brain. It acts as a basic mechanical and immunological protection.
15Inflammasome: a multiprotein complex that activates caspase-1 and -5 leading to the processing of pro-inflammatory cytokines IL-1β and IL-18 and cell death.
BOX 1. miRNA BIOGENESIS

miRNAs are small non-coding RNAs capable of silencing the expression of their target genes (49), they arise from a step by step biogenesis process which begins with the transcription of the miRNA gene by the polymerase II (Pol II) generating an RNA sequence of hundreds or thousands of bp called primary miRNA (pri-miRNA). The pri-miRNA is then processed by the microprocessor machinery composed of the type III RNAse Drosha and the Dgcr8 (DiGeorge syndrome critical region gene 8) protein, this processing results in a stem-loop secondary structure known as a precursor miRNA (pre-miRNA) which has ~70 base pairs of length. The pre-miRNA is exported from the nucleus to the cytoplasm by Exportin 5, and once in the cytosol it is processed by another type III RNAse called Dicer which finally generates an RNA duplex consisting of the mature miRNA and its corresponding complementary miRNA (miRNA*) (49-51). The mature miRNA is reeled to the RNA-induced silencing complex (RISC), where its effector protein Argonaute (Ago) conducts the silencing process that, depending on the degree of complementarity (high or low), results in target degradation or translational inhibition respectively (49, 50, 52). An important feature for the correct functioning of the miRNA is based on the degree of complementarity between the bases 2-8 of the 5’ end of the miRNA (which is defined as the seed sequence) and the 3’ untranslated region (UTR) of its target.

miRNA biogenesis pathway
miRNA and epigenetic regulation in HD

miRNA expression profiles of HD patients have shown an up-regulation of miR-29a and miR-132 and down-regulation of other miRNAs including miR-9/9*, miR-29b, and miR-124 (57, 58). It has been determined that REST\textsuperscript{16} and co-REST transcription factors are direct targets of miR-9 and miR-9* respectively (58). Htt has been shown to sequester REST in the cytoplasm, leading to an upregulation of REST target genes including Bdnf. REST also targets different miRNAs (miR-9, miR-24, miR-29 and miR-132) but their upregulation has not been studied in HD models (59, 60). mHtt cannot interact with REST, which correlates with the observation that in HD, REST targets are preferentially repressed (61). In HD patients, the inability of mHtt to sequester REST causes this transcription factor to be translocated to the nucleus leading to a decrease in neuronal gene expression (58). Apart from being a transcriptional regulator, REST can also function as an epigenetic regulator by the recruitment of different histone and chromatin modifying proteins to repress transcription including HDACs, H3K9 methyltransferases G9a\textsuperscript{17} and Suv39H1\textsuperscript{18}, H3K4 demethylase LSD1\textsuperscript{19}, and the Methyl-CpG binding protein MeCP2\textsuperscript{20}, among others (62, 63).

The polyglutamine repeat region of mHtt can bind the acetyl-transferase domain of CBP\textsuperscript{21} and P/CAF\textsuperscript{22} in a repeated dependent manner inhibiting their acetyltransferase activity, as well as that of p300\textsuperscript{23}, probably by sequestering them in aggregates (86). This causes a reduction in the global levels of H3 and H4 acetylation, which in turn leads to altered gene expression. Treatment with HDAC inhibitors can rescue the acetylation levels, ameliorate some of the symptoms, and inhibit or retard neurodegeneration in R6/2 HD mice models (87, 88). Htt can also interact with PRC2 and facilitate its activity (89). Htt null embryos present anterior streak and mesoderm patterning deficits that resemble those seen in PRC2 mutants, which are caused by a failure to repress

\textsuperscript{16}REST: RE1-silencing transcription factor is a transcription factor responsible for silencing neuronal genes in non-neuronal tissues.
\textsuperscript{17}G9a: a histonemethyltransferase responsible for mono- and dimethylation of lysine 9 of histone H3, a mark associated with transcriptional repression.
\textsuperscript{18}Suv39H1: Suppressor of variegation 3-9 homolog 1, is a histone methyltransferase that specifically trimethylates lysine 9 of histone H3, a mark associated with transcriptional repression.
\textsuperscript{19}LSD1: Lysine specific demethylase 1 is a histone demethylase responsible of removing methyl groups from lysine 4 and 9 of histone H3, therefore acting as a corepressor or coactivator respectively.
\textsuperscript{20}MeCP2: Methyl CpG binding protein 2 binds methylated CpG pairs and mediates transcriptional repression and the recruitment of corepressor proteins. Mutations are the main cause of Rett syndrome, a neurodevelopmental disorder.
\textsuperscript{21}CBP: CREB binding protein is a histone acetyltransferase that functions as a transcriptional coactivator of many transcription factors.
\textsuperscript{22}PCAF: P300/CBP-associated factor is a histoneacetyltransferase that normally associates with p300 and CBP to activate transcription.
\textsuperscript{23}p300: E1A binding protein p300 is a transcriptional coactivator that functions as a histone acetyltransferase.
BOX 2. EPIGENETIC MECHANISMS

Epigenetic mechanisms have arisen as an additional level of transcriptional regulation, and over the past years they have been implicated in different processes including different developmental programs, maintenance of pluripotency, differentiation, patterning, and in the development of different diseases. Epigenetic mechanisms can be defined as "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states" (64). Epigenetic information normally acts by regulating the state of the chromatin, switching between an "open" or transcriptionally permissive state and a "closed" or transcriptionally repressive state. These changes in the architecture of chromatin are regulated by different mechanisms including histone post-translational modifications (65), histone variants (66), chromatin remodelers (67), and DNA methylation (68).

Histone post-translational modifications occur primarily on the N-terminal tails of histones, these modifications include methylation, acetylation and ubiquitination, among others (65, 69). Acetylation normally occurs at different lysine residues of histone 3 and histone 4 (H3 and H4) and it is associated with an open chromatin state. Histone methylation also normally occurs on lysine residues of H3 and H4, though methylation on different residues has different effects on chromatin architecture. Methylation at H3 lysine 9 and at H3 lysine 27 (H3K9me and H3K27me respectively) are associated with a closed chromatin state while H3K4me is associated with an open chromatin state. Ubiquitination normally occurs in histones 2A (uH2AK119) and 2B (uH2BK120), and it is associated with repression and activation respectively. Acetylation marks are established by histone acetyl transferases (HATs) and are removed by histone deacetylases (HDACs). Among the most common HATs are CREB-binding Protein (CBP) and p300. HDACs, like the sirtuin family, are also capable of deacetylating non-histone proteins, playing an important role in their regulation (65, 69).

The Polycomb repressing complexes 1 and 2 (PRC1 and PRC2) are of the most studied chromatin remodelling complexes. PRC2 is a multi-subunit protein complex that represses transcription mostly by the establishment and propagation of H3K27me3 marks. Ezh2, a PRC2 subunit, is the protein responsible of establishing the H3K27me3 mark (70).

Another important epigenetic process is DNA methylation, which occurs through the addition of a methyl group to the 5 carbon of a cytosine residue in the context of a CpG dinucleotide, in vertebrates (71-73). DNA methylation is established by different DNA-methyl transferases (DNMT); DNMT3A and DNMT3B are known as de novo methylases as they can establish "new" methylation patterns (74); while Dnmt1 is known as a maintenance methylase as it is responsible for keeping the methylation patterns after replication (75). In most cases DNA methylation can repress transcription by two mechanisms: i) a transcription factor can fail to recognize its binding site if it is methylated (76), and ii) it can repress transcription by the recruitment of Methyl-DNA binding proteins (MBDs) that repress transcription by the recruitment of other proteins such as chromatin remodelers, among them HDACs (77). DNA methylation can also enhance transcription when the methylation occurs in the binding site of a repressor (78, 79).
PRC2 regulated Hox genes. Htt interacts with PRC2 subunits Ezh2 and Suz12 and is necessary for the establishment of H3K27Me3 levels. Interestingly, longer glutamine repeats (>23 residues) increase the global levels of H3K27Me3, this suggests that HD patients could present H3K27Me3 hypermethylation which could enhance a transcriptional deregulation. Also, levels of H3K9Me and ESET methyl transferase have been shown to be elevated in mouse models of HD and in HD patients (90).

Levels of H2A monoubiquitination (uH2A), associated with transcriptional repression, are increased in different regions of R6/2 mice brains including the striatum, hippocampus and cortex, and also at the promoter region of genes repressed in HD including Drd2 (dopamine receptor 2), Penk1 (proenkephalin) and Sst (somatostatin). Ring225 is the E3 ubiquitin ligase responsible of ubiquitinating H2A and its activity can be modulated by Bmi-1. Htt was found to bind more to Bmi-1 than to mHtt, which suggests that in HD Bmi-126 might be more accesible for binding DNA and regulating H2A ubiquitination. On the other hand, monoubiquitination of H2B, which is associated with a transcriptionally active chromatin, was found at very low levels in R6/2 mice

24ESET: SET domain bifucated 1 is a histone methyltransferase responsible for trimethylating lysine 9 of histone H3, associated with transcriptional repression.
25RING2: Ring finger protein 2 is a member of the Polycomb group of proteins that functions as an E3 ubiquitin ligase and mediates monoubiquitination of lysine 119 of histone H2A that is a mark of transcriptional repression.
26Bmi-1: BMI1 polycomb ring finger oncogene is part of the multiprotein Polycomb complex PRC1 and it is proposed to modulate RING2 activity.
and a decreased association of this mark was found in the repressed genes. Ring2 silencing led to lower levels of uH2A and an upregulation of some of the genes that were repressed. Ring2 silencing also leads to lower levels of H3K9 di- and tri-methylation, while hBre1\textsuperscript{27} silencing, the E3-ubiquitin ligase for H2B, leads to lower levels of H3K4 di- and tri-methylation (91).

Overall these results suggest that different mechanisms in HD result in a preferentially repressed chromatin state which in turn result in the aberrant expression of different genes to induce the pathology (Figure 2). Although these epigenetic changes have been associated to HD and even though an inflammatory component in HD has been reported, epigenetic mechanisms have not yet been linked to inflammatory pathways in this disease. Thus, it will be interesting to determine if deregulation of epigenetic events targeting inflammatory genes cooperate in the progression of HD.

**Multiple sclerosis**

Multiple sclerosis (MS) is a chronic, progressive disease that affects young adults, it is characterized by the presence of autoreactive CD4+ T cells, which are probably activated in peripheral organs by a yet unknown agent and then migrate to the CNS where they establish an immune response against myelin antigens (92). Myelin forms a sheath around axons in the central and peripheral nervous systems and allows the propagation of neuronal action potentials. In MS there is a decrease in the population of oligodendrocytes\textsuperscript{28} as a result of cytotoxic CD8+ T cell attack, which leads to demyelination, axonal damage and loss of neuronal function (92, 93). Several factors, including genetic DR15 haplotype of HLA (human leukocyte antigen) present in the Caucasian population as well as environmental factors such as smoking, vitamin D deficiencies and viral infections, have been established as risk factors for developing MS. However, the mechanisms leading to the loss of immunological tolerance\textsuperscript{29} and the emergence of autoimmunity in MS remain unknown. Recent studies have associated viral infections to the development of the pathogenesis in MS. The CD46 molecule functions as a receptor of human herpes virus 6. Interestingly, the complex CD3/CD46 of CD4+ T cells from MS patients increases the production of IL-1β and IL-17A (94). In accordance with this, varicella zoster virus particles have been found in the CSF of MS patients with episodes of remission and relapse (95). Furthermore, bacterial infections can also contribute to the development of MS. High

\textsuperscript{27}hBre1: homolog of S. cerevisiae BRE1 is a E3 ubiquitin ligase that mediates monoubiquitination of lysine 120 of histone H2B which is associated with transcriptional activation.

\textsuperscript{28}Oligodendrocytes: type of brain cell that provides support and insulate the axons in the central nervous system.

\textsuperscript{29}Immunological tolerance: unresponsiveness of the immune system.
Figure 2. Epigenetic regulation by Htt and mHtt. Upper panel: Wild type Huntington (Htt) participates in the regulation of different epigenetic processes in the cell. Htt can interact with PRC2 and is necessary for the establishment of H3K27Me3 levels. Htt has also been proposed to bind and regulate Bmi-1, which is responsible of regulating Ring2 and H2A ubiquitination. REST can also be sequestered in the cytoplasm by Htt, which leads to the expression of its targets. Lower panel: Mutant Huntington (mHtt) could enhance a preferentially closed chromatin state and transcriptional repression through different mechanisms. mHtt can bind and inhibit histone acetyl-transferases like CBP and p300, causing a reduction in the global levels of H3 and H4 acetylation. Also mHtt has been associated with higher H3K27Me3, H3K9Me and ESET methyltransferase levels. mHtt is unable to bind and sequester REST in the cytoplasm enabling REST to inhibit its targets.

Concentrations of autoantibodies against heat shock protein 70 (HSP70) have been found in the cerebrospinal fluid of patients with MS. These autoantibodies are generated due to the homology between HSP70 and bacterial protein DnaK. The presence of anti-HSP70 induces an increase in the expression of TNF-α and IL-8, contributing to the inflammatory process (96).

There are several hypotheses that establish microglia and astrocytes as the initiators of the autoimmune reaction in MS. It has been suggested that in early stages of the disease, even before the onset of symptoms, the presence of T cells that secrete IL-17 and IFN-γ in the CNS is responsible for the activation of microglia by inducing an inflammatory response. The activation of microglia
induces the demyelination of axons through the activation of phagocytosis, the release of ROS, NO, glutamate and TNF-α (97). The expression of TLRs is upregulated in experimental autoimmune encephalitis (EAE), a mouse model of MS, which contributes to chemokine production in microglia and astrocytes (98). Recently it was shown that TLR2 and MyD88 are essential for hyaluronan induced inhibition of oligodendrocyte precursor cells maturation and remyelination in vitro (99) contributing to the neurodegenerative process. Moreover, the blockade of Mac-1 (CD11b/CD18) and fibrin interaction in microglia is neuroprotective in EAE (100).

Neuroinflammation may be perpetuated in MS through several mechanisms. Myelin increases the expression of proinflammatory cytokines such as TNF-α, IL-1β and IL-6. Myelin can also interact with CR3 (complement receptor 3) and activate NF-κB in macrophages (103). It has recently been demonstrated, using NALP3 deficient mice, that the inflammasome formed by this receptor is activated by myelin oligodendrocyte glycoprotein (MOG), resulting in the activation of caspase-1, IL-1β and IL-18. Both cytokines are necessary for the differentiation of CD4+ T cells to the Th1 and Th17 phenotypes, which produce proinflammatory cytokines such as IFN-γ and IL-17, respectively. Additionally, NALP3-deficient mice are resistant to developing EAE (104), evidencing the importance of inflammation in the development and progression of this disease. The deposition of hyaluronan inhibits the maturation of oligodendrocyte precursor cells and remyelination process through the activation of TLR2 and MyD88 (99). Stathmin, a protein that is associated to the myelin sheaths, is capable of activating an inflammatory response in astrocytes and microglia that is dependent of TLR3 in MS (105). Together, these observations suggest a constant monitoring of the myelination process by components of the innate immune system.

Glutamate is the major excitatory neurotransmitter in the CNS, it promotes neural development, learning and memory. High concentrations of glutamate have been detected in patients with MS, caused by an exacerbated production by the active immune system cells and by a decrease in the number of glutamate transporters in astrocytes, which results in a toxic effect on oligodendrocytes and neurons (106). Administration of antagonists of
ionotropic glutamate receptors increases the survival of oligodendrocytes (107). However, the activation of metabotropic glutamate receptor 4 inhibits the development of Th17 cells in response to myelin antigens (108), suggesting that high concentrations of glutamate may represent a mechanism of negative regulation of the inflammatory response. These results open the possibility of new treatments to control MS.

**miRNAs and multiple sclerosis**

Different analyses have detected an abnormal expression profile of miRNAs in MS patients when compared to healthy individuals. For example, miR-34a, miR-155 and miR-326 are upregulated in MS. CD47 is a transmembrane protein with an important role in the regulation of macrophage migration and phagocytosis. CD47 is a direct target of miR-326, this interaction during MS promotes the differentiation of Th17 cells (109). Other correlative studies have shown that miR-18b, miR-599 and miR-96 are related to relapse and remission phases of MS (110).

Furthermore, differential expression of several miRNAs was detected in different cell types of the immune system and the expression of the same miRNA could be altered in different cell types during MS. One example of this is miR-17-5 that is down regulated in CD4+ T cells of MS patients (111), while it is upregulated in blood cells of MS patients (112).

In normal cellular conditions microglia are in a quiescent state characterized by a low expression of activation markers such as CD45 and components of the MHC class II. In contrast, in the EAE model, microglia become activated and contribute to the development of the disease (113). This could be explained in part by the down regulation of miR-124 in microglia as well as in CNS-infiltrating peripheral macrophages during the remission phase of the disease which suggest that the expression level of miR-124 is inversely correlated with the activation state of these cells in EAE and possibly in MS (113). Furthermore, the transcription factor CCAAT/enhancer-binding protein-α (C/EBPα) is a direct target of miR-124. Therefore, as miR-124 is down regulated in EAE, low levels of C/EBPα might lead to a reduced expression of its target PU.1 that consequently could lead to have lower levels of its target genes including CD45 and MHC class II genes (114). In addition, when bone marrow-derived macrophages are transfected with miR-124, there is a decrease in their proliferation rate and a down regulation of activation markers including CD45 and MHC class II genes. Moreover, after EAE induction in mice, the administration of miR-124 reduces microglial activation and leukocyte infiltration in the CNS, suggesting that miR-124 could act as an anti-inflammatory miRNA in MS and therefore could be considered as an important target for future therapeutic strategies (114).
Epigenetic component in MS

In EAE CD44\textsuperscript{30} has been shown to play a role in the differentiation of lymphocytes (115). It was observed that CD44 KO mice presented a reduction in the number of infiltrating CD4+ T cells, and had a preferential polarization for Th2 over Th1 after MOG activation. This phenotype was exclusively caused by a CD44 deficiency in T cells as transferred CD44+ cells caused disease progression, and mice deficient in CD44 only in CD4+ T cells were completely resistant to developing EAE. This polarized differentiation was caused by the demethylation of the il4/foxp3 promoter and an enhanced methylation of the ifnγ/il17a promoter in CD44 KO mice after stimulation with MOG, while CD44+ T cell activated with MOG present demethylation at the ifnγ/il17a promoter and methylation at the il4/foxp3 promoter.

A potential therapeutic target for MS could be HDAC9\textsuperscript{31} as it has been shown that HDAC9 also has a role in the regulation of T cell function (116). HDAC9 deficiency in mice results in an increased number of Treg cells in lymphoid tissues, which is associated with a resistance to develop colitis. HDAC9 deficiency also increases Th2 polarization by decreasing Th1 cytokines and the number of activated CD4+ T cells. Trichostatin A (an HDAC inhibitor) has been proved to decrease systemic autoimmunity in autoimmune mice models.

Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease worldwide. PD is characterized by the accumulation of cytoplasmic proteins, such as α-synuclein\textsuperscript{32}, in structures called Lewy bodies, which lead to the progressive loss of dopaminergic neurons in the substantia nigra\textsuperscript{33} and cerebral cortex (117). Dopaminergic neurons in this area control muscle movements, therefore the loss of these neurons causes resting tremors, rigidity and bradykinesia that are characteristic symptoms of the disease (118). Nitration of α-synuclein, a post-translational modification that takes place in a ROS and NO rich environment, prevents proteolysis of α-synuclein by both the proteasome-ubiquitin system and autophagy, resulting in the formation of

\textsuperscript{30}CD44: a cell surface glycoprotein that can function as a receptor for different ligands, including hyaluronic acid and osteopontin. It has been involved in different functions such as cell-cell interactions, cell adhesion, lymphocyte activation, and migration, among others.

\textsuperscript{31}HDAC9: Histone deacetylase 9 is a type IIA HDAC that shuttles between the nucleus and cytoplasm in response to different stimuli. It mediates the removal of acetyl groups from different substrate proteins including histones.

\textsuperscript{32}Alpha-synuclein: a presynaptic protein whose function in the healthy brain is currently unknown and is implicated in the phatogenesis of various neurodegenerative diseases.

\textsuperscript{33}Substantia nigra: a brain structure located in the midbrain and is an important motor center.
aggregates in the cytoplasm (119, 120). Genetic factors, such as polymorphisms in the promoter of α-synuclein, represent only a fraction of patients with PD. Currently there is data supporting the hypothesis that neuroinflammation is a major cause of neurodegeneration in PD (121). Several studies have confirmed the presence of TNF-α, IL-1β, IL-6, and IFN-γ in the CSF as well as post-mortem brains of PD patients (122, 123). Chronic overexpression of IL-1β and TNF-α exerts a toxic effect on dopaminergic neurons; also, polymorphisms in TNF-α and IL-1β increase the risk of developing PD (124, 125). Another factor that contributes to the death of dopaminergic neurons are the ROS produced by microglia as a result of α-synuclein phagocytosis (117).

On the other hand, it has been proposed that another risk factor for developing PD could be inflammation originated in peripheral organs (126). The concentrations of MCP-1, RANTES, MIP-1α, IL-8, IFN-γ, IL-1β and TNF-α are higher in peripheral blood mononuclear cells of patients with PD compared with healthy individuals. Interestingly, mononuclear cells of these patients also respond more strongly to bacterial components, such as LPS, than cells from healthy individuals (127). Accordingly, infectious diseases that present chronic inflammation, as infection of the gastric mucosa by Helicobacter pylori, increase the risk of developing PD (128). Evidence from a PD model of neurodegeneration, induced by the administration of 6-hydroxydopamine (6-OHDA), shows that the sole activation of microglia is not sufficient to induce the secretion of proinflammatory cytokines, but still an increase in IL-1α and IL-1β mRNA levels are observed (129). However this pre-activated microglia under the action of a second stimulus, such as infection, show an exacerbated proinflammatory phenotype that accelerates the development of the disease (130).

Several environmental triggers known to promote neuroinflammatory responses have been implicated in non-familial or idiopathic forms of PD, they include traumatic head injury, viral inflammation, exposure to heavy metals, organophosphate compounds, neurotoxins like the 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), and certain pesticides such as paraquat and rotenone (131-140). In addition to these factors, epidemiological research indicates that rural living, pesticide use, well-water consumption and certain occupations (including mining and welding), are associated with an increased risk of developing PD (141-143). However, and despite extensive search, it has not been possible to identify any causative environmental chemical agent in the etiology of PD. A number of mitochondrial and proteasomal toxins have been associated with clusters of atypical Parkinsonism (e.g. MPTP) and acute administration of these compounds has proven useful in providing experimental models of the disease. To date toxin
models have provided important clues about the potential mechanisms by which oxidative stress may contribute to nigrostriatal pathway degeneration. Although a comprehensive discussion of potential environmental triggers is beyond the scope of this chapter, we highlight here those non-genetic factors with strongest association to PD.

**miRNAs and PD**

Recent studies have shown miRNAs that could have a relevant role during PD pathogenesis. Within the miRNAs that possibly act during PD development are miR-7 [137] and miR-433 [138] that target α-synuclein and fgf20 respectively, which have been reported as key genes in PD pathogenesis. In this sense, it was demonstrated that over expression of miR-7 leads to a significant down regulation of α-synuclein in *vitro* and therefore, miR-7 could be used as a potential therapeutic agent for PD treatment. On the other hand, it was suggested that DNA variants within the fgf20 3’ UTR could affect the binding and affinity of miR-433 for this 3’ UTR and possibly generate a change in the expression of fgf20 that probably contribute to the PD pathogenesis. In this sense, Fgf20 administration was demonstrated to have an anti-inflammatory effect in animal models of colitis and small intestinal ulceration/inflammation (144). Therefore, it is possible that the gain of affinity of miR-433 for the fgf20 3’ UTR, exacerbates the inflammatory process of PD pathogenesis by decreasing Fgf20 levels.

**Epigenetic component in PD**

Mutations associated with PD in α-synuclein cause an increase in its nuclear localization. Nuclear α-synuclein (SNCA) can bind directly to histones causing reduced levels of acetylation and lead to neurotoxicity, which can be rescued by the use of HDAC inhibitors (145). SNCA has also been shown to interact and sequester DNMT1 in the cytoplasm (146). This correlates with a decreased 5-mC immunoreactive nuclei and a decreased nuclear localization of Dnmt1 in cortex samples of PD patients. Reduced methylation patterns have been found in the regulatory regions for α-synuclein, sepw1 and prkar2a, the later normally over expressed in PD brains. The expression of α-synuclein has been shown to be regulated by methylation in a region of intron 1 of SNCA (147). It has also been observed that dopamine, through its receptors, can lead to the demethylation of this region and an increase in SNCA mRNA levels (148). The inhibition of SIRT2, a class III HDAC, has been shown to rescue part of the neurotoxicity in a cellular model of PD, though this could be primarily mediated through SIRT2 citoplasmic targets (149).
Alzheimer's disease

Alzheimer's disease (AD), a progressive neurodegenerative disease, is the leading cause of dementia worldwide. AD is characterized by both synaptic loss and neuronal death as a result of extracellular and intracellular accumulation of β-amyloid deposits (βA) and neurofibrillary tangles (NFTs) in brain regions important for memory and cognitive processes (150). The formation of these deposits is the result of the processing of the amyloid precursor protein (APP). APP is a transmembrane protein that regulates neuronal activity, plasticity and memory (151). Under normal physiological conditions processing of APP is performed by α- and γ-secretases and this is known as the non-amyloidogenic pathway. However, the APP is subject to other processing mediated by β- and γ-secretases, resulting in the production of βA42 and βA40 peptides, this type of processing is known as the amyloidogenic pathway. βA42 peptides are highly unsoluble and form oligomers and fibrils with other peptides and proteins, constituting senile plaques (152). The accumulation of senile plaques causes axon damage, alters the structure of the cytoskeleton and finally induces neuronal death. Mutations in APP and in the subunits of the γ-secretase, presenilin 1 and presenilin 2 (PSEN1 and PSEN2), have been associated with familial forms of AD. The presence of the ε4 allele of apolipoprotein E has also been found to facilitate the deposition of the βA peptide (153). Additionally, the deregulation of CDK5 (cyclin dependent kinase 5), and its regulatory subunit p25, have been associated with the development of AD. CDK5 is capable of phosphorylating the microtubule-associated protein Tau, which inhibits its association with microtubules leading to the formation of NFTs. Mutations in Tau have also been described to promote the formation of NFTs (148). Still these mutations only constitute a small percentage of the cases of AD, where most of the patients do not present a mutation on these genes (154).

Many studies suggest that βA42 oligomers have a neurotoxic effect that is mainly characterized by the induction of ROS (155). High concentrations of IL-1β and IL-18 have been detected in brain tissue and plasma of AD patients, which suggests the presence of inflammation in the brain (61). Activation of microglia with βA peptides induces production of IL-1β and TNF-α, and increases the accumulation of βA peptide through a positive feedback loop by the activation of highly glycosylated receptor (RAGE) (156). There are several studies that have shown that TLRs play a central role in inflammation and neurodegeneration induced by βA peptides. An increase in mRNA levels of TLR2, TLR4 and TLR9 has been reported in microglia associated with βA plaques (157). Additionally, the production of proinflammatory cytokines
induced by βA fibrils in microglia is mediated by TLR2 (158). On the other hand, it has been observed that activation of TLR4 by βA peptides induces neuronal death by apoptosis (159). Also, the TLR4/TLR6/CD36 complex activated by βA fibrils can induce an inflammatory response (160). However, activation of TLRs can also have a beneficial effect. Recently it was reported that the intraperitoneal administration of ODNs (oligodeoxynucleotides), synthetic ligands of TLR9, in Tg 2576 mice (mouse model of AD) reduces amyloid deposits in the brain parenchyma. This is probably due to an increased number of macrophages and dendritic cells that migrate to the CNS, and therefore an increase in phagocytosis and elimination of amyloid deposits (161).

The production of IL-1β induced by βA peptides is correlated with a decrease in intracellular K+, a requirement for activation of the inflammasome (162), which induces the maturation and secretion of IL-1β. In accordance to this, in microglial cells βA oligomers induce the release of cathepsin B to the cytosol and activate the inflammasome formed by NALP3, ASC and caspase-1 (163). Altogether these evidences suggest that some of the neurotoxic effects could be generated through the activation of the inflammasome.

miRNAs and AD

In AD miR-146 has been reported to directly target the complement factor H (CFH) which limits the inflammatory responses in the brain. Therefore, while healthy individuals present basal levels of miR-146 and CFH, in AD patients the expression of this miRNA increases leading to a decrease in CFH levels resulting in an enhanced inflammatory process in the brain (164, 165). Moreover, NF-κB has been shown to directly activate the transcription of miR-146 (165) (Figure 3). Accordingly, it has been demonstrated that infection of human neural cells with the phenotypic reactivator (17syn+) of the Herpes simplex virus type-1 (HSV-1) induces the expression of miR-146 while downregulating CFH (166). Additionally, it has also been demonstrated that HSV-1-mediated infection correlates with the upregulation of proinflammatory mediadors such as the cytosolic phospholipase A2 (cPLA2), cyclooxygenase-2 (COX-2), and IL-1β (166). These data suggest that infections and stress may play a key role during AD development and progression by making neural cells more susceptible to produce and to mantain inflammatory responses.

Furthermore in AD patients upregulation of miR-146 has been demonstrated to correlate with the downregulation of the interleukin-1 receptor-associated kinase-1 (IRAK-1), an essential component of Toll-like/IL-1 receptor signaling (167). The stimulation of human astrocytes with IL-1β and βA peptides increases the levels of NF-κB, IRAK-2 and miR-146, which
Figure 3. miR-146 promotes chronic inflammation in AD. In normal individuals, the activity of NF-κB is normally regulated and thus the expression of miR-146 is moderated and maintains normal levels of complement factor H (CFH). However, in AD proinflammatory cytokines promote the activation of the NF-κB transcription factor, which in turn activates the transcription of miR-146 resulting in the inhibition of CFH, leading to chronic inflammation.

Contrast with the downregulation of IRAK-1 seen in AD patients (167). Bioinformatic analysis revealed that miR-146 has a putative binding site in the 3’ UTR of IRAK-1 (167), which suggests that in AD and astrocytes a dynamic gene expression network might be conformed by the NF-κB-mediated upregulation of miR-146, which in turn represses IRAK-1, entailing a neuroinflammatory process. It will be of relevance to define if the putative binding site for miR-146 on the 3’ UTR of IRAK-1 is functional in order to develop potential therapeutic strategies based on miR-146 silencing to restablish IRAK-1 expression during AD pathogenesis, thus diminishing neuroinflammation.

Epigenetic component in AD

The intracellular fragment formed in the processing of APP (AICD) has been shown to interact with the HAT TIP60, which is suggested to enhance
**BOX 3 PHYTOPHARMACEUTICALS AS A NEW THERAPEUTIC ANTIINFLAMMATORY STRATEGY**

Given that a common feature of neurodegenerative diseases is the presence of an inflammatory process, the use of therapies able to target multiple anti-inflammatory signaling pathways represents an attractive strategy. Accordingly, several studies have shown that phytopharmaceuticals possess secondary compounds with antioxidant, antiallergic, and anti-inflammatory activities such as, terpenes, phenolic compounds, glycosides, flavonoids and alkaloids (180). In contrast to synthetic pharmaceuticals based upon single chemicals, many phytopharmaceuticals exert their beneficial effects through the synergistic action of several chemical compounds that act either at single or multiple target sites associated with a specific physiological process (181). Linking plant biochemistry and physiology to human health. Among the phytocompounds, the polyphenols are ubiquitous secondary metabolites found in plants; epidemiological, clinical and animal studies support their role in the prevention of various pathologies including neurodegenerative, cardiovascular diseases and cancer (182, 183). Over 500 polyphenols have been identified and classified into different groups including: phenolic acids (e.g. chlorogenic acid), stilbenes (e. g. resveratrol), lignands (e. g. seco-isoclariciresinol); flavonoids [flavonols (e.g. kaempferol, quercetin); flavones (e.g. apigenin, luteolin); isoflavones (e.g. daidzein, genistein); flavanones (e.g. hesperetin, naringenin); flavanols (e.g. (+)-catechin, (−)-epicatechin, epigallocatechin, epigallocatechingallate and anthocyanidins (e.g. pelargonidin, cyanidin, malvidin).

Experimental and epidemiological data suggest that polyphenols can ameliorate age-related cognitive development, and show neuroprotective effects against PD and AD. Administration of catechins present in green tea reduces deposition of βA peptides in a murine model of AD (184). Moreover, they also increase the plasticity of synapses in the hippocampus (185). Catechins can also exert neuroprotective effects in models of amyotrophic lateral sclerosis (186) and PD (187). Flavonoids are known to regulate inflammatory responses through inhibiting iNOS, COX-2 and down regulating the expression of NF-κB and C-reactive protein (CRP) (188, 189). They can also inhibit pro-inflammatory (IL-1β, IL-6, IL-8 and TNF-α) or increase anti-inflammatory (IL-10) cytokine secretion (190).

Recent findings suggest that polyphenols could interact with cellular signaling cascades regulating the activity of transcription factors (NF-κB and activator protein-1) (191-193) and consequently affecting the expression of genes in different organs including the brain; this ability resides on the capacity of some of these compounds to pass through the BBA (194). Different polyphenols present in phytopharmaceuticals inhibit DNMTs reactivating genes silenced by aberrant methylation (195). In addition, in vivo administration of specific polyphenols (catechin, anthocyanin or curcumin) to obesity animal model, the ApoE knockout mouse, reduces the atherosclerosis pathology, which correlates with a modulatory effect on the expression of specific miRNAs (192). Further, in vitro studies have demonstrated in LPS stimulated human blood monocytes or THP-1 monocytic cells, resveratrol another polyphenol, up-regulates miR-663 which exerts an antiinflammatory action via AP-1 transcriptional activity regulation (196).
Neurodegenerative disorders and inflammation

Gene transcription (168). It also may be involved in the acetylation of H4 required for DNA repair, which might help explain the increase in double strand breaks observed in AD patients and AD models (169). Mutant alleles of PSEN1 present an aberrantly high activity of CBP as they are not able to cleave N-cadherin to release its intracellular domain CTF2 which in turn promotes the degradation of CBP through the ubiquitin-proteosomal system (170). On the other hand, reduced levels of CBP have been reported in the cortex of PSEN1 and PSEN2 double knockout mice (171). In another neurodegeneration model, embryonic cortical neuron death can be induced by activating the APP signaling pathway. These neurons present lower levels of CBP and H3Ac (172). AD mouse models present lower levels of H4Ac after contextual fear conditioning, which correlate with a poor performance compared to WT mice. Treatment with the HDAC inhibitor Trichostatin A (TSA) improved the learning deficits in the mouse model of AD compared to WT mice (173). In p25/Cdk5 neurodegeneration mouse models p25 can interact and inhibit HDAC1 which results in double strand breaks and neurotoxicity, overexpression of a catalytically active HDAC1 diminishes the double strand breaks and neurotoxicity (174).

In AD mouse models of vitamin B deficiency, PSEN1 and BACE (β-secretase) promoters are found to be hypomethylated, which correlates with an increase in their expression. Administration of S-adenosylmethionine (SAM), which is the methyl donor used by DNMTs, has been shown to reduce PSEN1 and BACE expression (175, 176). DNMT3A and DNMT3B were also found to be downregulated in the same AD model (177). Also a reduction in DNMT1 activity has been reported in primate models of AD, which might correlate with the hypomethylation found in PSEN1 and BACE (178). Murine cerebral endothelial cells treated with βA 1-40 present reduced levels of global DNA methylation. In contrast the promoter of the metalloproteinase nephrilysin (NEP), which has been shown to play a role in the clearance of βA, was found to be hypermethylated, which is consistent with lower levels of NEP mRNA and protein (179).

Concluding remarks

Currently, neurodegenerative diseases are considered multi-factorial disorders due to the wide range of factors (including genetic, non-genetic and environmental factors) that participate on their origin and development. However, an inflammatory component has recently been proposed to be a common feature between certain neurodegenerative disorders such as Huntington's disease, multiple sclerosis, Parkinson's disease and Alzheimer's disease. Here we have described that during an inflammatory condition, the
blood brain barrier is capable of allowing the passage of immunocompetent cells to the brain to contend with this stress and also, that neuronal cells are capable of mounting an inflammatory response in these diseases. Different pro-inflammatory cytokines, such as IL-1β and TNF-α, are some of the signals that contribute to the neurodegeneration process by activating inflammatory pathways in neurons and glia. Still, in some of these diseases it is still unclear whether neuroinflammation is a triggering cause or a secondary effect of the neurodegeneration.

Interestingly, the population of neurons that is lost during these diseases is not the same. This could be explained by regulatory mechanisms that participate in each particular etiology, including epigenetic mechanisms (histone modifications and DNA methylation) but also, sncRNAs such as miRNAs, whose expression is altered during neurodegeneration. We also discuss some of the mechanisms by which these miRNAs participate in the development of an inflammatory condition, as well as how different epigenetic mechanisms lead to altered gene expression which is characteristic of these diseases. This information could be used for future therapeutic strategies, in which miRNA-containing nanoparticles could be designed in a cell type specific manner to deliver their particular cargo. Likewise, recent studies have shown that compounds such as flavonoids and polyphenols extracted from different plants, posses anti-inflammatory activity. Interestingly, part of this capacity results from the ability of these compounds to regulate particular miRNAs that at the end promote an anti-inflammatory effect. Taking advantage of powerful molecular biology techniques, it will be interesting to determine if additional miRNAs and molecules involved in both the immune response and in epigenetic processes are target of specific phyto-pharmaceuticals resulting in an anti-inflammatory effect. This information would help to develop phytopharmaceuticals as multicomponent mixture drugs to improve their therapeutic efficacy. Finally, this strategy could constitute an alternative to prevent or treat chronic diseases with an inflammatory component.

References

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