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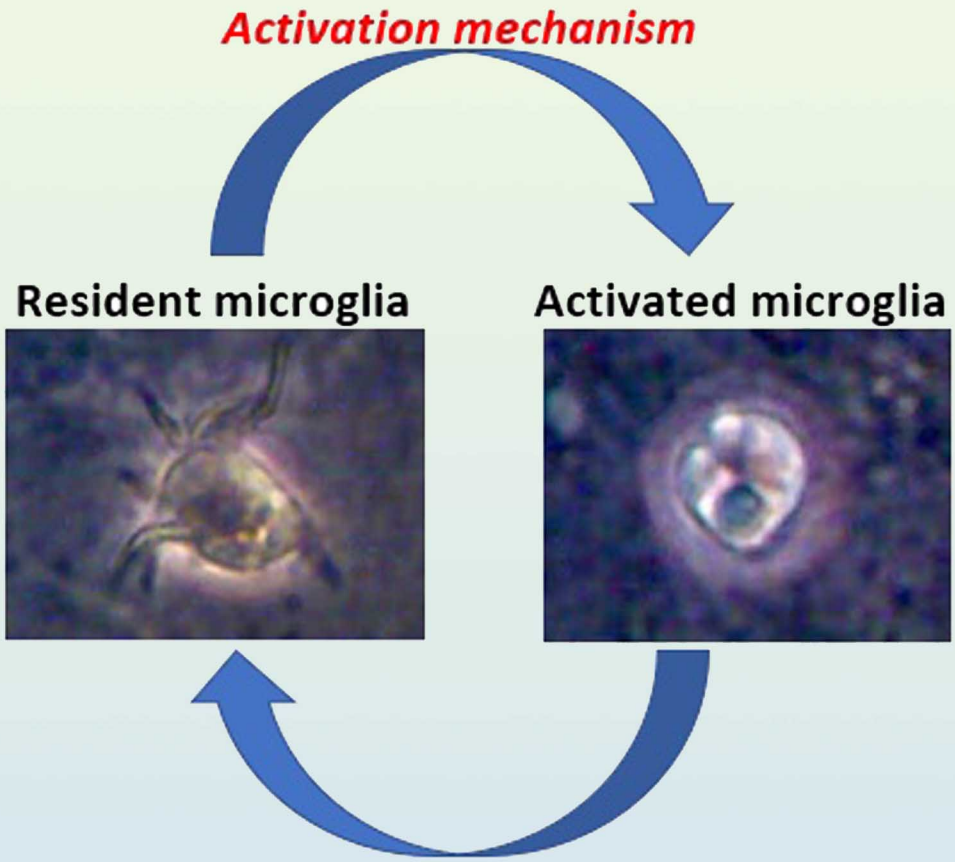

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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

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B- Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C- Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

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Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

REVIEW ARTICLE

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Microglia and its role in neurodegenerative diseases

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Abstract

Microglia are immune cells colonized in the central nervous system (CNS) during the development of the embryo. They make up about 12% of the glial cell population in the brain. These cells play an important role in eliminating the damage that may occur in the CNS or in carrying out normal functions. Microglia, which are in morphologically inactive form, are characterized by small cell body, small amounts of cytoplasm and cellular extensions that are released towards the environment. They undergo a significant morphological change and switch to the active form in a pathophysiological condition in the CNS, and they have the ability to migrate to the damaged area by ameboid movement. In today's studies, microglia in the active form has been stated to show neuroprotective and neurotoxic effects in neuronal structures in addition to carrying out phagocytosis of metabolic residues in the medium. It has also been mentioned in recent studies that microglia located in the CNS have a highly sensitive activation mechanism against inflammation and pathological conditions. Understanding the microglial activation mechanism in neurodegenerative diseases is thought to may contribute to the diagnosis / treatment of neurological diseases as well as being a diagnostic marker for the etiology of the diseases. In this review, the general characteristics and activation mechanism of microglia and their functional roles in Alzheimer's, Parkinson's, epilepsy and multiple sclerosis diseases were discussed.

Keywords: Microglia, Alzheimer's Disease, Parkinson's, Epilepsy, Multiple Sclerosis

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List of Abbreviations;

AD, Alzheimer's disease; **ATP,** Adenosine triphosphate; **Aβ,** Amyloid-βeta; **CSF,** Colony-Stimulating Factor; **CSN**, Central nervous system; **EEG,** Electroencephalography; **GM,** Granulocyte macrophage; **IFN-γ,** İnterferon gamma; **LPS,** Lipopolysaccharides; **M,** Macrophage; **MAPK,** Mitogen-activated protein kinase; **MPTP**, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; **MS,** Multiple sclerosis; **NF-κB,** Nuclear factor-kappa B; **NO,** Nitric oxide; **PD**, Parkinson's disease; **PET,** Positron emission tomography; **ROS,** Reactive oxygen species; **SE,** Status epilepticus; **TSPO,** Translocator protein

Introduction

Microglia

Microglia are immune cells of the central nervous system (CNS) and functionally involved in pathological and physiological disorders (Kettenmann et al., 2011). These cells entered the literature for the first time by the German psychiatrist Frank Nissl (19th century) via mentioning their phagocytic and migratory properties as a result of his neuropathological studies (Nissl, 1899). The term "mesoglia" was used by W. Ford Robertson to describe phagocytic factors of mesodermal origin, and the term “neuroglia” was used by Virchow to describe microglial bodies in the same period (Virchow, 1856). Microglia were studied in detail by Pio del Rio-Hortega in 1932, and the points highlighted by the Rio-Hortega were that microglia entered the CNS in the early development process and these ameboid cells with macrophage characteristics were of mesodermal origin. In the CNS, microglia, the cells waiting in an inactive form with their small bodies and cellular extensions released towards the environment while resting, can undergo a morphological transformation and migrate to that point by taking on the amyloid structure, when they perceive the physiological or pathological condition as a threat (Dheen et al., 2007; Boche et al., 2013). With advanced imaging systems in recent years, migration, proliferation and phagocytosis, which are among the distinctive characteristics in a pathological stage, can be observed either in *in vitro* or *in vivo* studies (del Rio-Hortega, 1932). In addition, the perception that glial cells have only “filling function” in the CNS has changed, and it has been reported in the literature that glial cells were affected by substances such as neurotransmitters, antibodies, cytokines, chemokines and have neuroprotective and neurotoxic effects on neuronal structures (Streit and Kincaid-Colton, 1995; Volterra and Meldolesi, 2005).

Discussions about the origin of microglia have continued for a long time. Although some scientists have suggested that microglia are of hematopoietic origin due to their phenotypic similarity to peripheral monocytes, macrophages and dendritic cells (Hess et al., 2004), it is now thought that the cells are of mesodermal origin and the microglia found in the CNS were formed by macrophages produced in yolk sac being differential (Menassa and Gomez-Nicola, 2018). It was stated that microglia were derived from circulating monocytes and reached the brain through the circulation in a postnatal animal study using antibodies (Perry et al., 1985). It has been determined that the form change time of the cells slows down with increasing age, and the cells can switch to the active form very quickly and gain phagocytic properties in cases such as trauma or infection in early ages (Zhang et al., 2007). The numerical density of microglia can change in the CNS depending on healthy and diseased conditions (Perry and Holmes, 2014). Although some studies are available in the literature stating that there are subgroups of microglia, these studies are still unclear (Bertolotto et al., 1998). The common view is that functional subgroups of microglia appear under pathological conditions (Clausen et al., 2008; Shimizu et al., 2008). The markers used in the definition of microglia are especially important in the identification of the cells in histopathological studies. Today, markers are used for the detection of microglia according to their functional forms; however, a single molecular marker that does not label environmental macrophages is not readily available (Schmid et al., 2009; Villani and Peri, 2019). Furthermore, secondary microglial cell lines have become popular for researchers in order to understand their roles in neurodegenerative diseases. However, criticisms that microglia are not modeled correctly can be encountered in the literature (Timmerman et al., 2018). An important reason why this negative view on secondary cell lines is common is that "immortalization" significantly affects the biology of a cell (Horvath et al., 2008; Henn et al., 2009).

Morphology and physiology of microglia

Microglia have been realized to play an important role in neuronal diseases in the studies conducted to better understand the damage occurring in the CNS. Although time-interval morphological examinations were carried out in the early days, the detection of inactive microglia in neurocortex in *in vivo* studies with the development of two-photon imaging techniques was an important turning point (Sun et al., 2019). The stages of transition from inactive to active form were determined in ongoing studies, and the cell was observed to withdraw the branches of branched bodies in this process (Figure 1). *In vitro* studies have shown that inactive microglia can be found in different forms rather than a single phenotype (for example: 2- or 3-pole or rod-shaped), and morphological appearance may vary depending on the type of movement (Lampron et al., 2013). In addition to the importance of rapid and massive morphological

change, it has been stated in some literature that the relationship between the ameboid appearance and active phenotype will not always yield correct results as a different approach (Markovic et al., 2009). Rather than the morphological appearance of the cells, the use of molecular markers specific for cell activation status has been argued to provide better results in identifying microglia (Villani and Peri, 2019). Considering the issues to be taken into account in the markers and methods to be used, they should distinguish microglia from other neuronal cells (astrocytes, oligodendrocytes and neurons), monocyte or macrophage structures. It is among the issues to be considered whether the marker to be used will separate all microglia regardless of the status or according to their active / inactive status (Choudhury et al., 2020).

Studies conducted to understand the physiological characteristics of microglia are generally *in vitro* studies. It is difficult to see microglia with ameboid properties in the inactive form in *in vitro* medium. Microglia can be stimulated in culture medium, and obtaining proinflammatory phenotype provides a wide area of study. Lipopolysaccharides (LPS) or incubation with stimulants such as interferon gamma (IFN-γ) are classic methods for activating microglia. The detection of the release of many proinflammatory agents, such as TNF-α, IL-6 or nitric oxide is among the important parameters in understanding the activation mechanism (Minogue et al., 2012). However, the protocol differences on microglia, especially the differences in *in vivo* protocols in the literature make it difficult to use precise statements about the physiology of these cells.

Microglia activation mechanism

Microglia turns into an active form especially in cases of infection, trauma, ischemia, neurodegenerative diseases and excessive neuronal activity (Boche et al., 2013; Saijo et al., 2013). In the activation mechanism, it is triggered by the cellular interaction, induction of membrane molecules, intracellular enzyme change and proinflammatory agents (Kierdorf and Prinz, 2013b). Morphological differences were observed in cases of changes in the physiological and pathological conditions of microglia in histopathological studies. Structural differentiation in microglia provided the basis for the introduction of the concept of microglial functional plasticity in the 1980s and is still valid today (Streit et al., 1988). Microglia are responsible for the phagocytosis of extracellular molecules apart from the phagocytosis of apoptotic bodies. Besides, microglia functionally involve in synaptic conduction and synapse activity, which have an important role in the CNS (Kettenmann et al., 2013). In addition to this neuroprotective property, it has also been observed that synapses exposed to microglia for a long time in pathological conditions have been destroyed. As stated in the studies, microglia may affect synaptic plasticity directly or indirectly (Cullheim and Thams, 2007).

Microglia are distinguished according to morphology and gene expression in healthy conditions. At this stage, their immunological phenotype is characterized by low expression of major histocompatibility complex proteins and other antigen surface receptors. This phenotype is much more opposite compared to other macrophages that are more readily in the active form. One of the reasons for this condition has been associated with the absence of serum proteins that have been shown to cause macrophage activation of the brain (Lull and Block, 2010). Microglia can also be stimulated in non-pathological conditions. An example of this is the removal of residues in the medium after apoptosis and normal cell death, especially during brain development through phagocytosis. They are also responsible for removing foreign materials such as plaque, which can damage cells on extracellular surfaces. Microglia surrounding neurons can provide trophic support to neurons through the release of nerve growth factors, neutrophils and other neurotrophic factors (Elkabes et al., 1996). Recently developed microscope records showing that microglia are dynamic cells, they constantly scan their microenvironment and can respond instantly to the slightest change have been visual evidence in *ex vivo* and *in vitro* studies (Stence et al., 2001).

Molecules triggering microglial activation

Microglia switch to the active form by creating an inflammatory response to molecules formed in any damage to the brain. The purpose of activation is to achieve homeostasis in the CNS (Papa et al., 2016). Since microglia are dynamic, the activation process is associated with the proliferation of the cells and multiple reactive microglial phenotypes (Streit, 2002; Nimmerjahn et al., 2005). In addition to the phenotypic change in activated microglia, the increase in the cell population is accomplished by migration to the site of damage and

secretion of pro- or anti-inflammatory cytokines, chemokines, growth factors and oxidative stress-inducing molecules (Figure 2). If there is a neuronal death, they act as macrophages and remove cellular debris with phagocytosis (Graeber and Streit, 2010).

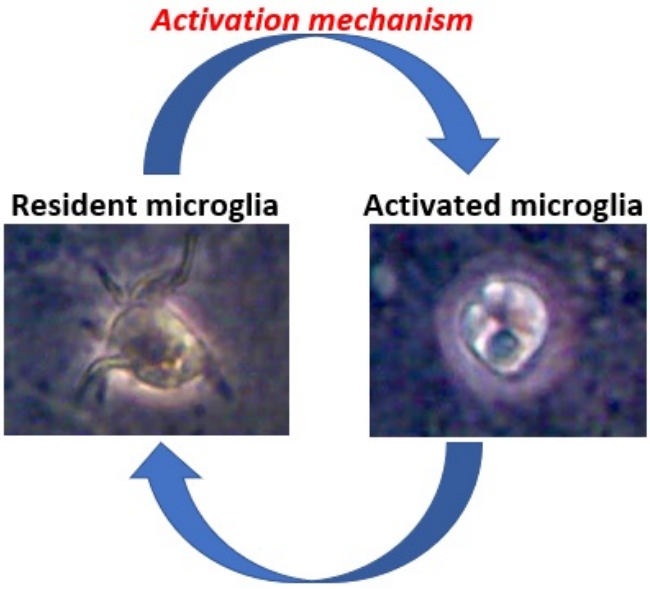

Figure 1. *Microglia, the cells waiting in an inactive form with their small bodies and cellular extensions released towards the environment while resting, can undergo a morphological transformation and migrate to that point by taking on the amyloid structure, when they perceive the physiological or pathological condition as a threat.*

Many studies have been conducted to understand the molecules responsible for microglial activation and the pathways that these molecules activate (Raivich et al., 1999; Hung et al., 2017; Xu et al., 2018). Microglia have been thought to play a triggering role in electrical changes caused by neuronal damage and ion changes around the damaged neurons in molecular activation in *in vivo* studies(Quagliato and Nardi, 2018), while some studies have indicated that activation occurs by low molecular weight active molecules (peptides, hormones, etc.) (Park and Chun, 2017; Bast et al., 2018). There are also studies mentioning the effects of microglia on growth factors and cytokines (Macrophage (M) -CSF, granulocyte macrophage (GM) -CSF) (Parajuli et al., 2012). Calcitonin gene-related peptide and ATP are accepted as activators in the facial nerve transection model (Priller et al., 1995). Microglia are thought to be a biological response for increased ATP production, chemotaxis, molecules such as TNFα and IL-1β (Lambert et al., 2010). It has been found that when microglial activation is achieved with LPS, ATP release occurs, and this stimulates the "P2Y1R" receptor found in astrocytes. The P2Y1R receptor has been emphasized to have an important role in the physiopathology of many brain diseases by modulating "metabotropic glutamate receptor 5" (Pascual et al., 2012). It has been reported in the literature that there are also some neurotransmitter-sensitive receptors expressed in microglia. Glutamate, GABA, Purinergic, Adenosine, Cholinergic, Cannabinoids, Adrenergic, Dopamine, Opioid and Neuropeptides can be given as examples of neurotransmitters that affect microglial activation (Pocock and Kettenmann, 2007). While studies on molecules regulating rapid microglial activation are ongoing, it is thought that some transcription factors have an effect on phenotypic change of the cell. Among them, factors such as Runx-1, Irf8 and Pu.1 inside the cell and CD200, CX3CR1 and TREM2 outside the cell have been reported to play a role in activation in the literature (Kierdorf and Prinz, 2013a).

The role of microglia activation in the Alzheimer's disease (AD), Parkinson's disease (PD), epilepsy and Multiple sclerosis (MS)

Microglia located in the CNS are very sensitive to inflammation and pathological conditions. Morphologically activated microglia, like other tissue macrophages, appears in different phenotypes depending on the nature of the tissue damage. Microglial response to damage suggests that these cells can be considered as diagnostic markers of disease onset or progression and may contribute to the diagnosis / treatment of diseases caused by neuronal damage (Ransohoff and Perry, 2009). The persistence of microglia activated after acute injury and in chronic disease indicates that these cells have an innate immune memory of tissue damage and degeneration. The microglial phenotype is also modified by systemic infection or inflammation. Evidence from some preclinical models shows that systemic manipulations can improve disease progression; however, the data from other models suggest that systemic inflammation exacerbates disease progression (Hanisch and Kettenmann, 2007; de Haas et al., 2008).

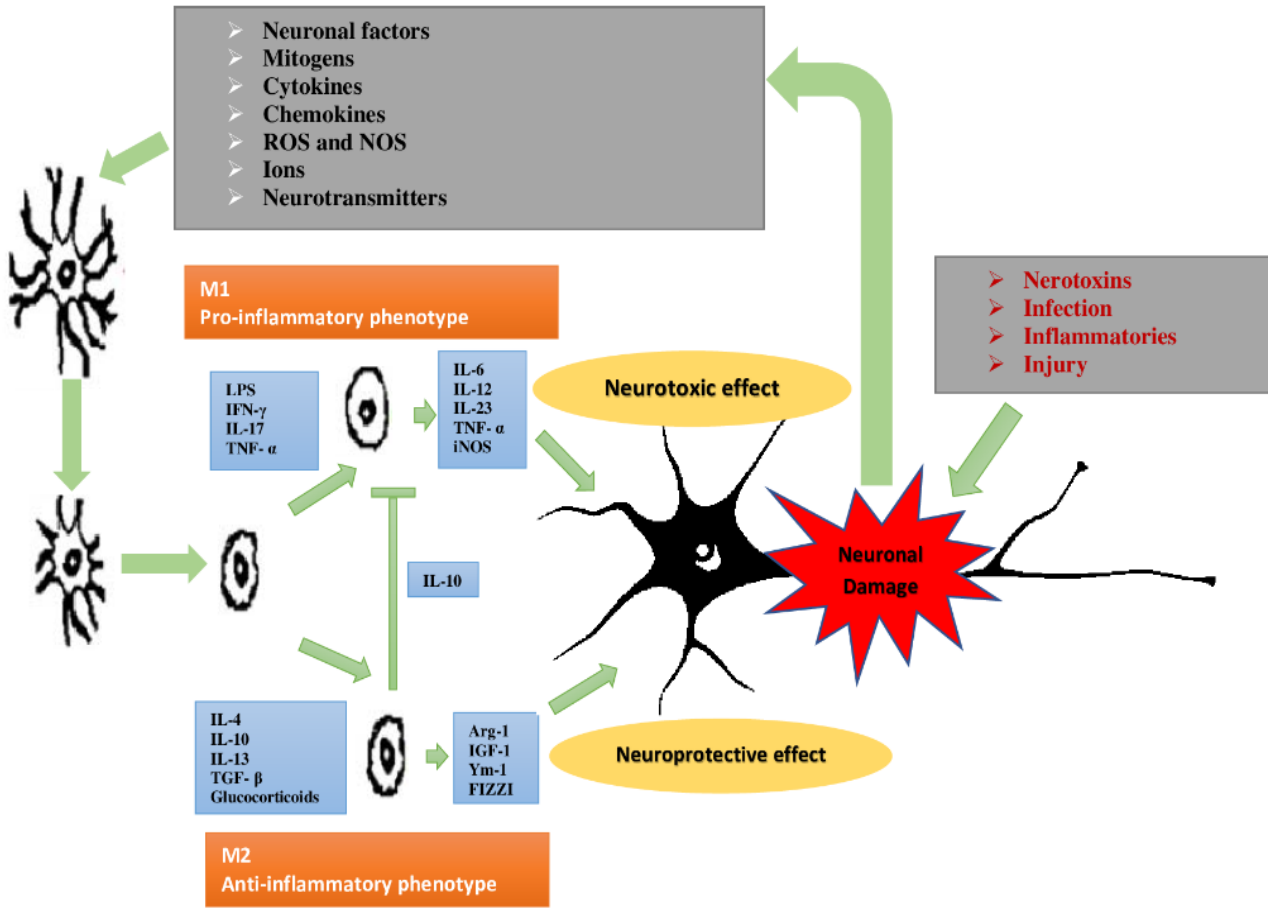

Figure 2. *Activation mechanism of microglia against neuron damage. Microglia phenotype may vary depending on damage. M1 cells have a neurotoxic effect on neuron while M2 cells have a neuroprotective effect.*

Understanding the relationship between microglial activation and the etiology of the most frequently observed neuronal diseases such as AD, PD, MS and epilepsy will be important for the diagnosis / treatment methods to be used in these diseases.

AD and Microglia

AD is the most common neurodegenerative disease that starts with memory loss, forgetfulness and progresses with behavioral disorders in the patient, especially with increasing age (Lane et al., 2018). When the pathology of the disease is examined, it is characterized by senile plaques formed by aggregation of amyloid-βeta (Aβ) 1-42 and / or Aβ1-40 plaques occurring when the amyloid precursor protein is incorrectly cut by β-secretase and γ-secretase, and neurofibrillary tangles formed by hyperphosphorylation of tau protein (Ossenkoppele et al., 2015). In addition to its toxic effect on neurons, Aβ accumulation provides microglial activation owing to the receptors in microglia. Activated microglia show neurotoxic properties and secrete proinflammatory cytokines. Microglia have been stated to provide elimination of neurons by two-photon imaging in mice with AD (Wang et al., 2018). It has been stated that microglia have a neuroprotective effect in the first stages of AD, by being involved in elimination of Aβ accumulation by phagocytosis; however, overactivated microglia have been emphasized to may cause neurodegeneration in the later stages of the disease. Clinical studies conducted also support this (Hamelin et al., 2016; Fekete et al., 2018). There are studies stating increased expression levels of some enzymes in microglia in relation to AD. The RIPK1 enzyme from microglia has been stated to be increased as an inflammatory response in AD, triggering the neuronal death mechanism. (Ofengeim et al., 2017). It has been mentioned that

increasing the phagocytosis function in microglia by using the functions of the existing receptors can prevent Aβ accumulation and even reduce overactivation in the study on disease-related increase in Aβ to increase cell activation by binding to microglial membrane receptors. For this reason, the functional roles of microglial membrane receptors should be taken into consideration while aiming therapeutic targets for AD (Yu and Ye, 2015; Chen et al., 2016). Imaging can be performed about microglial activation in the disease process by using imaging techniques. It was stated in an *in vivo* mouse study that obtaining images using positron emission tomography (PET) imaging of the Translocator protein 18 kDa (TSPO) will lead to a significant improvement in the follow-up of the disease process (Hamelin et al., 2016; James et al., 2017). There are studies in the literature stating that proliferation and activation of microglia cause neurodegeneration. There are also studies suggesting that the use of receptor inhibitors that trigger these mechanisms can slow AD progression. The study using the "colony-stimulating factor 1 receptor (CSF1R)" inhibitor (GW2580) found in human microglia supports this idea (Olmos-Alonso et al., 2016). TREM2 is a transmembrane protein that is selectively expressed by microglia in the central nervous system, and its determination in cerebrospinal fluid is promising for the diagnosis of neurodegenerative disorders. Suarez-Calvet mentioned in their study that the change in TREM2 level in the disease process can provide information about cell death and microglial activation (Suarez-Calvet et al., 2016). In their *in vivo* study, Heneka et al. stated that it created a chronic inflammatory response in Aβ-induced microglial activation, and they associated it with the loss in the phagocytic properties of microglia, especially in synaptic dysfunction from "Nod-like receptor protein 3 (NLRP3)" (Heneka et al., 2013). Lee et al. argued that non-steroidal anti-inflammatory drugs (ibuprofen and aspirin), antioxidant (GSH) and anti-inflammatory cytokine IL-10 administration would be beneficial in AD in their *in vitro* study examining the effects of anti-inflammatory treatment modality on human neuroblastoma cells (SH-SY5Y) (Lee et al., 2015). It was mentioned that the use of the substance with known anti-inflammatory properties against Aβ-induced neurotoxicity could be a potential therapeutic approach by alleviating tau hyperphosphorylation in a different study on SH-SY5Y cell line (Yeo et al., 2018). In fact, it has been stated in the literature that microglia showing overactivation in neurodegenerative diseases can be suppressed with anti-inflammatory drugs (Gan et al., 2015). "Trans-caryophyllene", known for its antioxidant properties on Aβ-induced cells, was observed to have positive effects in reducing microglial activation in the study performed on secondary BV-2 microglial cell line (Hu et al., 2017). Also, the similar positive effect of "Loganin", a different anti-inflammatory and an iridoid glycoside derived from *Cornus officinalis*, was observed in a similar study (Cui et al., 2018).

PD and Microglia

PD is a neurodegenerative disease characterized by movement disorders. Pathological findings are the loss of dopaminergic neurons in substantia nigra and a-synuclein plaques (Goetz, 2011). Proinflammatory cytokines are assumed to trigger microglial activation in serum and cerebrospinal fluid of patients (Sanchez-Guajardo et al., 2015). The death of dopaminergic neurons activates microglia, and activated microglia are thought to accelerate disease progression. It has also been noted that α-synuclein involved in the pathogenesis of the disease activates microglia (Sanchez-Guajardo et al., 2015). It is known that many genes responsible for pathological conditions in the brain, especially motor neuron disease, are expressed in microglia (Haenseler et al., 2017). In their study, Yang et al. found the "P2Y6" receptor, which contributes to the activation and phagocytic properties of microglia. They stated that this receptor could be a clinical biomarker for PD, and a therapeutic approach to the disease thanks to receptor blockers (Yang et al., 2017). It is reported in the literature that progressive degeneration of dopaminergic neurons is further increased with excessive increase in microglial cell activation (Wang et al., 2017). A significant relationship was found between serum samples from PD and low vitamin D levels. Oral administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), which is a vitamin D derivative, was observed to slow down neuroinflammation in an animal study (Calvello et al., 2017). Jonnson et al. observed that the extract used reduced the cytotoxicity of BV-2 and SH-SY5Y caused by oxidative stress and inflammation, as well as reducing dopaminergic neurotoxicity in the study in which the extract of *"Mucuna pruriens"* plant considered as anti-PD was used in BV-2 microglial and human SH-SY5Y

neuroblastoma cells (Johnson et al., 2018). “CD200”, one of the cell surface transmembrane glycoproteins, is stated to be closely associated with microglial activation, PD pathogenesis and progression. Knowledge of such membrane receptors will shed light on future treatment modalities (Wang et al., 2007). Dynamic changes in the production of proinflammatory cytokines such as tumor necrosis factor have been investigated in the mouse model study of PD created by MPTP. In addition, CD206 was measured in microglia to better characterize the changes in microglial cell phenotype. A linear relationship was detected between dopaminergic degeneration and microglial activation as a result of the study (Pisanu et al., 2014). The prominent pathological feature of PD is dopaminergic neuron loss. A flavonoid (Licochalcone A) isolated from licorice has been shown to may reduce dopaminergic neuron loss by reducing microglial activation in an *in vivo* and *in vitro* study of LPS-induced PD models (Huang et al., 2017). Mitochondrial dysfunction, oxidative stress and excessive formation of reactive oxygen species play an important role in neurodegeneration. In their clinical study, Jucaite et al. used the “AZD3241”, the inhibitor of “myeloperoxidase”, which is an enzyme that is expressed in microglial cell and produces ROS, and noted its positive effect (Jucaite et al., 2015). The main therapeutic approaches related to PD are intended to intervene neuroinflammation. Isobavachalcone is the main component of Psoralea corylifolia. It was observed to specifically reduce interleukin expression and inhibit the nuclear factor-kappa B (NF-κB) pathway in BV-2 secondary cell line in a mouse induced by MPTP in an in vivo study. As a result, substances that would reduce neuroinflammation were emphasized to have clinical potential for PD (Jing et al., 2017). TSPO was stated to increase due to inflammation in a different study. Neuroinflammation was attempted to be determined using PET in an in vivo study. In this study, it was stated that overactivation of microglia due to inflammation occurred in the early stages of the disease and it remained stable in the following process (Ghadery et al., 2017). It was stated in a study investigating the potential effect of glutaredoxin-1 regulation on dopaminergic viability in the central nervous system that glutaredoxin-1 regulation caused neuroinflammation and consequently promoted neuronal cell death and increased dopaminergic loss (Gorelenkova Miller et al., 2016). Yan et al. investigated the effect of “idebenone” which is a coenzyme Q10 analog and known for its antioxidant properties in their in vivo and in vitro study of MPTP-induced PD. BV-2 cells were activated with LPS in the study. As a result, idebenone was observed to decrease proinflammation in LPS-induced BV-2 cells and activation of the MAPK and NF-κB signaling pathways (Yan et al., 2018).

Epilepsy Disease and Microglia

Epilepsy is a chronic disease with complex pathology, characterized by repeated seizures. epilepsy is thought to occur as a result of synchronous abnormal discharge of intracranial neurons (Snoeijen-Schouwenaars et al., 2017). The disease, which can be seen in every person regardless of age, affects more than 50 million people worldwide, especially in terms of quality of life, social, behavioral and economic aspects. Electroencephalography (EEG) is considered the most important tool for evaluating a patient with epilepsy. It is possible to confirm the type of seizure and predict the epileptogenic area in the brain with the help of EEG (Guerreiro, 2016). Epileptic seizures can be induced using the necessary blockers for the inhibition or activation of synaptic and voltage-sensitive ion channels (Staley, 2015). In chronic epilepsy, increased microglial activation can cause neuroinflammation due to persistent seizures (Qin et al., 2007; Loane et al., 2014). In a study, microglial activation and inflammation-related neuronal damage due to the "Notch signal" were investigated in rats in which epilepsy was created. Western blot, RT-PCR, immunohistochemistry and immunofluorescence results showed that the Notch signaling played an important role in neuroinflammation and inflammation-related neuronal damage in epilepsy and might become a new potential therapeutic agent for epilepsy with future supportive studies (Wu et al., 2018). Status epilepticus (SE) is a serious neurological condition. It has been mentioned in animal studies that SE may cause hyperactivation in hippocampal neurons related to seizure frequency (Schartz et al., 2018). In a recent study, glial cell activation was noted to be important in the development of epilepsy, and high-mobility group box-1was found to have an effect on glial cell activation through Toll-like receptor 4 / NFκB signaling pathway in epileptic seizures (Shi et al., 2018). Current studies emphasize that microglial activation plays an important role in the pathophysiology of epilepsy. The effect of

antiepileptic drugs was investigated in the study creating an inflammation model in primarily obtained astrocyte and microglia. At the end of the study, the antiepileptic drugs used were expressed to regulate the overactivation of glial cells, as they reduced permanent inflammation (Dambach et al., 2014). Temporal lobe epilepsy is one of the most common types of persistent epilepsy and is characterized by periodic and unpredictable occurrence of seizures. Glial cell activation and proliferation, a pathological feature defined in this type of epilepsy, can alter blood-brain barrier integrity and ion and neurotransmitter homeostasis, causing an inflammatory response that results in neuronal hyperexcitability and seizure activity. The H19 gene, found in the central nervous system, has been reported to be overexpressed in glioblastoma tissue and promote proliferation, differentiation, migration and invasion of glioma cells. It was stated in an epileptic animal model study that the H19 gene was effective on microglial activation, and overactivation could be changed through this gene in future therapeutic studies (Han et al., 2018). Active microglia are known to have the ability to migrate to the damaged area in the brain tissue. In particular, chemokines, which can pass through the blood-brain barrier, are thought to activate this migration mechanism. For example, it is thought that there is a relationship between "CC chemokine receptor 5" and microglial migration. The detection of chemokines that contribute to the migration mechanism may be a potential target in reducing neurodegeneration that will occur, including the decrease in the activation and proliferation of microglia in future therapeutic studies (Louboutin and Strayer, 2013).

MS and Microglia

MS is an autoimmune disease characterized by chronic inflammation and demyelination in the CNS (Nicholas and Rashid, 2013). The etiology of the disease includes environmental and genetic factors. MS can be clinically distinguished from relapsing-remitting multiple sclerosis, secondary progressive multiple sclerosis, primary progressive multiple sclerosis, and progressive-relapsing multiple sclerosis. MS can be defined as benign MS or malignant MS depending on the severity of the signs and symptoms. The diagnosis of MS is based on criteria associated with characteristic lesions demonstrated by clinical-magnetic resonance imaging, cerebrospinal fluid analysis, and visual evoked potentials (Kaminska et al., 2017). Today, advanced imaging techniques and improvements in neuropathology are the results of lesions occurring with the initial stage of MS disease, axonal degeneration and neuronal deaths. The CNS actually tries to produce mechanisms to balance axonal loss; however, excessive degeneration causes irreversible neurological injuries (Correale et al., 2017). MS can be a pathological result of a triple interaction: inflammation, overactivation of microglia and demyelination (Popescu and Lucchinetti, 2012). Especially, overactivation of microglia is directly related to demyelination (Choi et al., 2012). Understanding the microglial activation mechanism in MS can shed light on therapeutic approaches, preventing the progression of the disease by neuroprotection, myelin repair and restoration of axonal activity and conduction via reducing harmful proinflammatory function (Airas et al., 2018). The detection of microglial activation in the brain of MS patients using *in vivo* PET imaging provides important information about MS pathogenesis and microglial activation (Ratchford et al., 2012). A better understanding of microglial activation in MS disease and of the genetic and epidemiological aspects of MS will be the most important step in the treatment of MS disease (Baecher-Allan et al., 2018). The effect of "Fingolimod", the first oral drug in MS treatment, was investigated in terms of the difference between the duration of neuroinflammation in an *in vivo* rat study. PET images obtained in the study showed that neuroinflammation reduced in the treatment group in parallel with the reduction of microglial activation (Vallez Garcia et al., 2017). In another study, it was stated that Fingolimod suppressed microglial activation in the in vitro model (Jackson et al., 2011). An animal study conducted to investigate the presence and underlying mechanisms of hippocampal dysfunction in experimental MS showed that the increase in proinflammatory cytokine level and excessive neurotoxic ROS increase triggered microglial activation and as a result, neurodegeneration occurs in the groups with MS. The idea of understanding the role of microglia in the mechanism and of the inhibition of activation was emphasized in the treatment of MS (Di Filippo et al., 2016). In an in vivo study, PET images showed increased microglial activation around the chronic lesion in MS (Airas et al., 2015). The literature also emphasized that further studies are needed to develop markers suitable for both in vitro and in vivo uses to help relate phenotypic

and functional properties of disease-related cells in order to understand the etiology of MS (Vowinckel et al., 1997). Clinically, there is no drug to regulate microglial activation in MS. In a study on this subject, which was conducted based on the inhibitory effect of "Dipyridamole" used as an anti-inflammatory agent on phosphodiesterase activity, dipyridamole was observed to normalize macrophage / microglial activity and to decrease the severity of experimental autoimmune encephalomyelitis (Sloka et al., 2013). It was argued that the suppression of cytokines and chemokines and reduction of NO production could prevent neuroinflammation observed in MS in an in vitro study using “Cyclopentenone prostaglandin” known as a potent anti-inflammatory agent capable of inhibiting macrophage and microglial activation (Storer et al., 2005).

Conclusions and Future Directions

Pathophysiological changes, microglial proliferation and activation are known to be increased in the CNS with the inflammation seen in neurodegenerative diseases (Colonna and Butovsky, 2017). However, current studies are still insufficient to understand the complex activation mechanism of these cells. Studies have shown that there is a close relationship between active microglia and the damaged area of the brain in neuropathology; however, their contribution to the disease process and neurodegeneration is still not fully understood (Sasaki, 2017). Although there are views arguing that cytokines secreted by microglia in the activation process have neurotoxic effects on neurons, different views suggesting that neurotrophic factors secreted by the cell have neuroprotective effects on the damaged cell are available (Du et al., 2017). The common belief about microglia is that they produce functional responses to diseases and damage occurring in the CNS thanks to their ability to show phenotypic change against the signals around them by performing continuous CNS scans, which makes these cells important.

As a result, the monitoring of microglial activation in the damage to occur in the CNS can be an indicator for the onset and course of the disease. In addition, it will be important to consider microglia in a therapeutic approach for neuronal diseases in the studies to be conducted on neurodegenerative diseases.

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