

Role of neuroinflammation in neurodegenerative diseases (Review)

WEI-WEI CHEN, XIA ZHANG and WEN-JUAN HUANG

Department of Neurology, Xuzhou Central Hospital, Xuzhou, Jiangsu 221009, P.R. China

Received December 17, 2015; Accepted February 29, 2016

DOI: 10.3892/mmr.2016.4948

Abstract. Neurodegeneration is a phenomenon that occurs in the central nervous system through the hallmarks associating the loss of neuronal structure and function. Neurodegeneration is observed after viral insult and mostly in various so-called 'neurodegenerative diseases', generally observed in the elderly, such as Alzheimer's disease, multiple sclerosis, Parkinson's disease and amyotrophic lateral sclerosis that negatively affect mental and physical functioning. Causative agents of neurodegeneration have yet to be identified. However, recent data have identified the inflammatory process as being closely linked with multiple neurodegenerative pathways, which are associated with depression, a consequence of neurodegenerative disease. Accordingly, pro-inflammatory cytokines are important in the pathophysiology of depression and dementia. These data suggest that the role of neuroinflammation in neurodegeneration must be fully elucidated, since pro-inflammatory agents, which are the causative effects of neuroinflammation, occur widely, particularly in the elderly in whom inflammatory mechanisms are linked to the pathogenesis of functional and mental impairments. In this review, we investigated the role played by the inflammatory process in neurodegenerative diseases.

Contents

1. Introduction
2. Sources of neuroinflammation
3. Neurodegeneration-induced neuroinflammation
4. Conclusion

1. Introduction

The degeneration of the central nervous system (CNS) is characterized by chronic progressive loss of the structure and

functions of neuronal materials, resulting in functional and mental impairments (1). While the causes associated with neuronal degeneration remain poorly understood, the incidence of neurodegeneration increases with age, in mid-to-late adult life (2). This phenomenon, which mainly affects elder individuals (3,4), occurs in neurodegenerative diseases such as Alzheimer's disease (AD), multiple sclerosis (MS), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS) following viral infections. Viruses are able to directly injure neurons by direct killing or induction of apoptosis (5) to leading to neurodegeneration (6,7). Similarly, in MS, the pathological features involve the permeability of the blood brain barrier (BBB), the destruction of myelin sheath, damage of the axon, the formation of glial scar and the presence of inflammatory cells, mostly lymphocytes infiltrated into the CNS (8). The loss of myelin is manifested in clinical symptoms together with neuropathic pain, paralysis, muscle spasms and optic neuritis (9).

Neurodegeneration induced by viruses, is noteworthy since it refers to the interaction between the CNS and environmental and viral factors, and suggests an important role of immune response in neurodegeneration (10). Immune activation in the CNS, always present in viral infections, immune-mediated disorders, and neurodegenerative diseases (11), involves microglia and astrocytes (12) which constitute the resident immune cells of the CNS and play an important role in the regulation of homeostasis of the brain during development, adulthood and aging (13). In the CNS, microglia constantly survey the microenvironment by producing factors that influence surrounding astrocytes and neurons (14), particularly in response to pathogen invasion or tissue damage thereby promoting an inflammatory response that further engages a self-limiting response through the immune system and initiates tissue repair (15). However, inflammation in tissue pathology that may result in the production of neurotoxic factors amplifying the disease states, indicates the persistence of inflammatory stimuli or failure in normal resolution mechanisms (16,17). Accordingly, specific inducers of inflammation associated with neurodegenerative diseases converge in mechanisms responsible in the sensing, transduction and amplification of the inflammatory processes that result in the production of neurotoxic mediators, such as cytokines and interleukins (18,19). These neurotoxic mediators are, in general, associated with several neurodegenerative diseases including AD, MS, PD and ALS, which are commonly linked to intracellular mechanisms such as the degradation of protein, the dysfunction of mitochondria, the defects of axonal transport and apoptosis (20-22). Inflammation associated

Correspondence to: Wen-Juan Huang, Department of Neurology, Xuzhou Central Hospital, 199 Jiefang South Road, Xuzhou, Jiangsu 221009, P.R. China
E-mail: rrj325@163.com

Key words: cytokines, astrocytes, astroglia, neuroinflammation, neurodegeneration

with AD, MS, PD and ALS is not typically the initiating factor of neurodegenerative disease. However, the emerging evidence on the sustained inflammatory response associated with the contribution of microglia and astrocytes in disease progression, suggest contributory important roles of effectors of neuroinflammation in neuronal dysfunction and death. In this review, we assessed the role played by these inflammatory processes in neurodegenerative diseases.

2. Sources of neuroinflammation

Vascular dementia and neuroinflammation. The cellular and molecular mechanisms of neuroinflammation are likely the same in aging and metabolic diseases such as hypertension, diabetes, depression, dementia or after cerebral insult such as stroke (23), and are considered as silent contributors of neuroinflammation (Fig. 1). In the elderly, inflammatory mechanisms have been associated with the pathogenesis of dementia and functional impairment. Systemic and local CNS inflammation significantly contributes to cerebral small vessel disease (SVD)-vascular dementia (24,25), hypothesized as microvascular changes that result in a state of chronic hypoperfusion, leading to continuous oligodendrocyte death and the consecutive degeneration of myelinated fibers that increase low-grade inflammation amplification of the risk of stroke (26). Another major risk factor for stroke and CNS tissue destruction is atherosclerosis, the disease of arteries that is characterized by vascular inflammation occasioned by the infiltration of monocytes into the injured vascular wall and an increase of interleukin (IL)-6 associated with future intracranial large artery stenosis progression after a stroke episode (27). Additional markers of inflammation such as C-reactive protein (CRP), which are well established in cardiovascular disease as strong predictors of subclinical and clinical atherosclerosis and progression of hemorrhagic stroke, were identified in SVD (28-31). Furthermore, adipose tissue dysfunction identified in obesity and hypertension, contributes to chronic and low-grade inflammation, predisposing to type 2 diabetes mellitus (DM) and cardiovascular disease (32,33) and could determine a worse outcome in stroke patients (34). Mortality in DM is primarily attributed to micro- and macro-vascular complication as well as sensory neuropathic complications, exacerbating the consequences of vascular disease. Sensory neuropathy promotes foot ulcers and abrogates warning symptoms during a heart attack. However, metabolic inflammatory disease (metaflammation) (35) occurring in unhealthy nutritional habits, can lead to a series of disorders and diseases such as CVD, stroke, hypertension, insulin resistance, metabolic syndrome and DM. Lipid hormone (sphingolipids and eicosanoids), cytokines and adipokines play an important role in metaflammation through the induction of adverse regulatory responses in target cells such as macrophages.

Depression and neuroinflammation. Normal aging is associated with an increase in the expression level of systemic inflammatory factors (36) such as pro-inflammatory cytokines (37-39). In the brain, this age-associated inflammation manifests initially as the chronic activation of perivascular and parenchymal macrophage/microglia expressing pro-inflammatory cytokines together with an increased number of astrocytes (40).

Accordingly, the chronic activation of pro-inflammatory signals in aging may contribute to an increase in vulnerability to neuro-psychiatric disorders (41). In obese women, the inflammation state was associated with a higher concentration of pro-inflammatory markers including IL-6, CRP and adipokines (42). These pro-inflammatory markers correlated positively with symptoms of depression and anxiety (43). Anxiety was alleviated with the reduction of inflammation following the surgical removal of fat tissue (44). In agreement with those findings, metabolic diseases such as obesity, hypertension, and being elderly are prevalent risk factors of depression, cognitive dysfunction and dementia (45) and there is an increase onset risk of aging-related diseases affecting the cardiovascular, cerebrovascular, neuroendocrine, metabolic, and immune systems in patients suffering major depression (46,47).

Although biological mechanisms of depression are poorly understood, conventional antidepressant treatments procuring beneficial effects were unsuccessful on one-third of depressed patients due to the inflammation that contributed to treatment resistance (48). The putative mechanism linking inflammation and depression involved oxidative stress, elevated pro-inflammatory cytokines IL-6 and IL-8 (49), endothelial nitric oxide synthase uncoupling and hyperglutamatergia. Accordingly, indirect evidence of neurovascular dysfunction have been found in major depressive disorder (MDD) (50,51), a severe psychiatric illness that is associated with increased levels of inflammatory markers in periphery, depression and mortality from suicide (52). Therefore, inflammatory markers identified in neurodegenerative diseases including MDD cover chemokines, adhesion molecules, cytokines and acute phase proteins (53).

Infections and neuroinflammation. Dynamic immune and inflammatory responses result from several offences in the CNS, of which infection is one (54). A virus can enter the CNS through two distinct hypothetical mechanisms, including hematogenous dissemination by which the virus gains access to the brain by BBB (55), and neuronal retrograde dissemination (56). However, it has been suggested that a virus can replicate in macrophage and CCR5⁺ T cells inside of the CNS in relation to the development and progression of dementia (57), as is the case for HIV proteins gp120 (58) and Tat (59) which are respectively able to induce the apoptosis of neurons through the enhancement of CXCR4-PKC (58), and to cause neuronal dysfunction through the disruption of miRNA expression (59). Most importantly, as in the case of HIV infection, other viral insults are associated with highly secreted cytokines, cholesterol increase, elevations of lipopolysaccharide (LPS) concentration, insulin resistance, testosterone deficiency and APOE4 (60), which are all involved in inflammation of the CNS.

Thus, inflammatory responses appear as the prevalent triggering mechanism driving tissue damage that is likely associated with different age-related diseases, as age-dependent upregulation of the inflammatory response is a consequence of chronic stress.

3. Neurodegeneration-induced neuroinflammation

The CNS is an immune-privileged organ with the innate and acquired immune response being closely controlled in relation

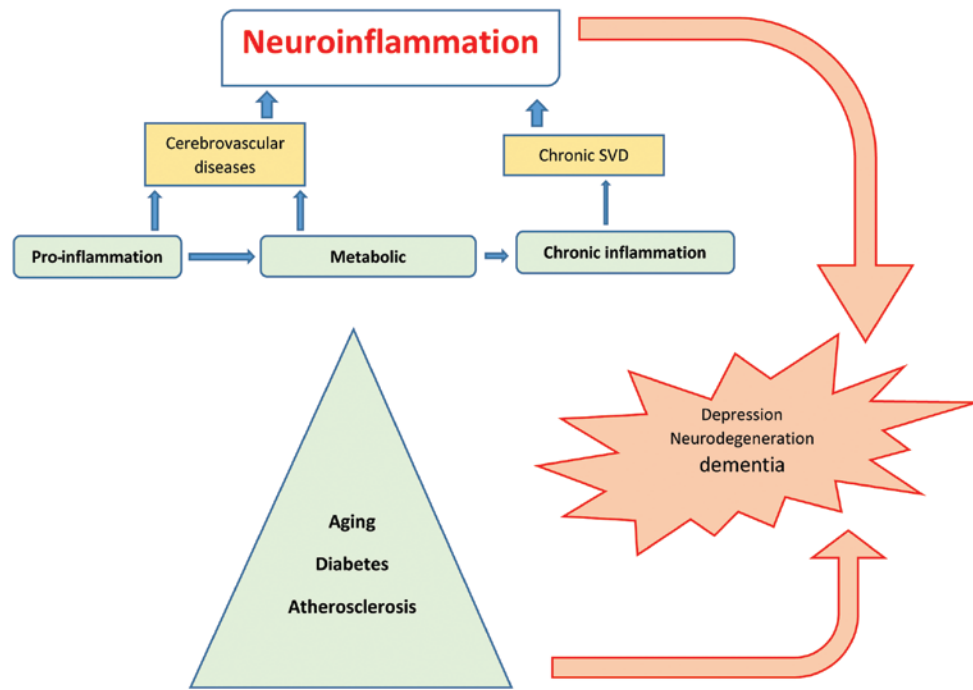


Figure 1. Sources of neuroinflammation. Aging, metabolic diseases and viral infections are sources of inflammation that can affect vessels and neurons, leading to neurodegeneration. SVD, small vessel disease.

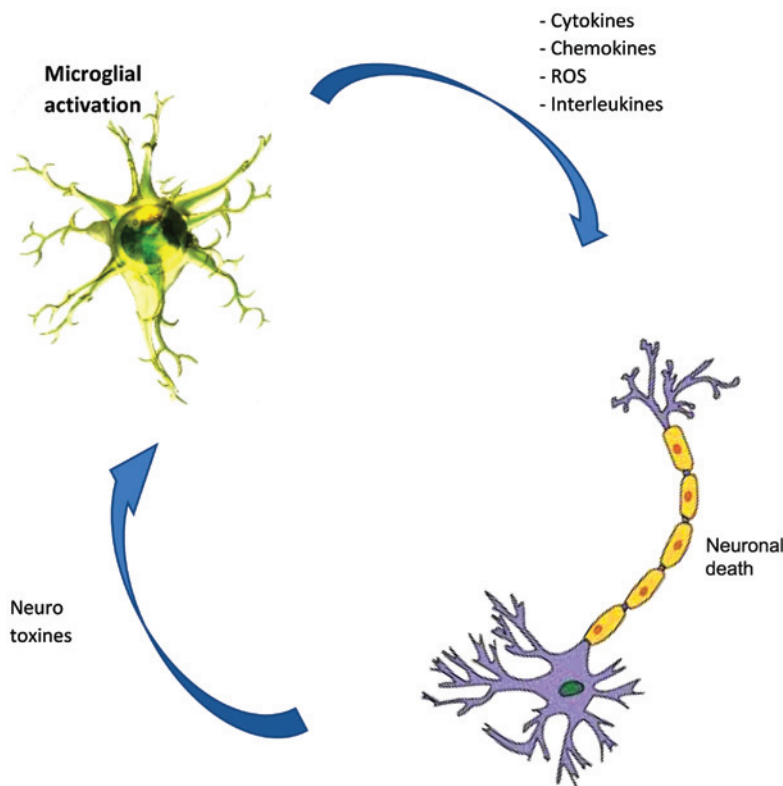


Figure 2. Relationship between microglial activation and neuronal death. Microglial activation may result in the release of neurotoxicity or neuroprotection. The increase of neurotoxic molecules favours neuroinflammation or neuronal death leading to neurodegeneration. ROS, reactive oxygen species.

with the periphery. Evidence suggests that a strong inflammatory response in the periphery from systemic LPS (61) or viral infections (62) results in the subsequent infiltration of leukocytes from the periphery to the CNS with consequent

neuroinflammation and neurodegeneration. An offense is followed by the initial activation of microglia, which induce the release of pro-inflammatory mediators that favour the permeabilisation of the BBB. The subsequent infiltration of peripheral

leukocytes occurs inside of the CNS, including T cells and macrophages, which share several functional features with microglia (61) including, the expression of toll-like receptors (TLRs), and consequently the ability to be activated by aggregated proteins or pathogen-associated molecular patterns (61,63); the expression of class II major histocompatibility complex, and the ability to present antigens to CD4⁺ T cells to exert an influence on the functional phenotype of T cells (64); as well as the ability to polarise their functional phenotype towards inflammatory M1 and anti-inflammatory M2 phenotypes, which can be influenced by inflammatory T cells and the lymphocyte regulatory T cells (65). Therefore, subsequent permeability of BBB leads to the possibility that peripheral macrophages can acquire a relevant role in the outcome of neuroinflammation. Accordingly, the alteration of CD4⁺ and CD8⁺ T cells has been observed in the periphery of neurodegenerative disease patients, suggesting a persisting antigenic challenge and that T cells may play a role in neurodegenerative diseases. Of note, the ratio of CD8⁺ to CD4⁺ T cells or the shift to a Tc1/Th1-type immune response may contribute to a harmful brain inflammatory reaction, and the presence of antibodies against neuronal antigen observed in neurodegenerative diseases (some of them being pathogenic), solidify the involvement of the immune system in neurodegenerative diseases (5). Consequently, an acute neuro-inflammatory response is beneficial to the CNS, minimizing the injury by activating the innate immune system (66,67). By contrast, chronic inflammation is characterized by the long-standing activation of microglia that sustained release of inflammatory mediators, leading to an increase of oxidative and nitrosative stress which perpetuate the inflammatory cycle (68), further prolonging inflammation (54,69), which is detrimental for several neurodegenerative diseases (70).

However, cell factors that influence microglial fate invade the epithelial cells of the BBB while T cells infiltrate the CNS, astrocytes and neurons (71), the most abundant glial cell population of the CNS which also participates in the innate immune response, triggered as a consequence of constant insult during inflammation or infection. Astrocytes are reservoirs of HIV-1, playing significant role in virus-mediated neurodegeneration (17,57). Accordingly, chronic neuroinflammation and microglia activation play central roles in the pathophysiology of neurodegenerative disease. For example, IL-1-positive activated microglia, colocalized with amyloid β plaques and neurofibrillary tangles in AD or present in degenerative motor neuron regions in patients suffering ALS (72) lead to abnormal phosphorylation of τ (73). Similarly, neurotropic viruses trigger long-term neuroimmune activation to underlying mechanisms of viral neurodegenerative diseases (74). Furthermore, neuroinflammation has been associated with either the cause or consequence of chronic oxidative stress, a key feature of all the neurodegenerative diseases that causes genetic structural alteration, lipid and protein, resulting in neurodegeneration. Microglial cells are the main source of reactive oxygen species and nitrogen species, tumor necrosis- α and glutamate, all of which are neurotoxic when released at a high dose after the activation of microglia (71,75,76) (Fig. 2), likely due to the stimulus from TLRs through the aggregated proteins (77,78) as is the case of AD patients (79), (MS) (9), PD (80), and ALS (81).

4. Conclusion

Neuroinflammatory disorders are conditions involving the immune response damage component of the nervous system. In the CNS, inflammatory effectors derived from innate and acquired immune systems as well as glial cells, particularly, microglia, act as sensors for disturbed brain tissue homeostasis and accumulate locally in response to neuronal cell injury or foreign entry in the brain; the differential activation of microglia cells being the central point that regulates neuroinflammation, which results in neurotoxicity or neuroprotection. The environmental exposure is therefore, the critical element for the fate of neurons with regard to degeneration or protection. Additional studies must be undertaken to benefit from the versatility of microglia, since activated microglia can also produce anti-inflammatory mediators and neurotrophic factors such as insulin-like growth factor-1, glial cell-derived neurotrophic factor, brain-derived neurotrophic factors and other factors (82-84), and procure beneficial effects.

References

1. Campbell IL, Krucker T, Steffensen S, Akwa Y, Powell HC, Lane T, Carr DJ, Gold LH, Henriksen SJ and Siggins GR: Structural and functional neuropathology in transgenic mice with CNS expression of IFN- α . *Brain Res* 835: 46-61, 1999.
2. Hof PR and Mobbs CV (eds): *Handbook of the neuroscience of aging*. Elsevier/Academic Press, Amsterdam, pp1-53, 2010.
3. Yuan J and Yankner BA: Apoptosis in the nervous system. *Nature* 407: 802-809, 2000.
4. Przedborski S, Vila M and Jackson-Lewis V: Neurodegeneration: What is it and where are we? *J Clin Invest* 111: 3-10, 2003.
5. Amor S, Puentes F, Baker D and van der Valk P: Inflammation in neurodegenerative diseases. *Immunology* 129: 154-169, 2010.
6. Shinya K, Shimada A, Ito T, Otsuki K, Morita T, Tanaka H, Takada A, Kida H and Umemura T: Avian influenza virus intranasally inoculated infects the central nervous system of mice through the general visceral afferent nerve. *Arch Virol* 145: 187-195, 2000.
7. Reinacher M, Bonin J, Narayan O and Scholtissek C: Pathogenesis of neurovirulent influenza A virus infection in mice. Route of entry of virus into brain determines infection of different populations of cells. *Lab Invest* 49: 686-692, 1983.
8. Jadidi-Niaragh F and Mirshafiey A: Histamine and histamine receptors in pathogenesis and treatment of multiple sclerosis. *Neuropharmacology* 59: 180-189, 2010.
9. Chastain EM, Duncan DS, Rodgers JM and Miller SD: The role of antigen presenting cells in multiple sclerosis. *Biochim Biophys Acta* 1812: 265-274, 2011.
10. Czirr E and Wyss-Coray T: The immunology of neurodegeneration. *J Clin Invest* 122: 1156-1163, 2012.
11. Ransohoff RM and Perry VH: Microglial physiology: Unique stimuli, specialized responses. *Annu Rev Immunol* 27: 119-145, 2009.
12. Perry VH and Teeling J: Microglia and macrophages of the central nervous system: the contribution of microglia priming and systemic inflammation to chronic neurodegeneration. *Sem Immunopathol* 35: 601-612, 2013.
13. Schwartz M, Kipnis J, Rivest S and Prat A: How do immune cells support and shape the brain in health, disease, and aging? *J Neurosci* 33: 17587-17596, 2013.
14. Sofroniew MV and Vinters HV: Astrocytes: Biology and pathology. *Acta Neuropathol* 119: 7-35, 2010.
15. Wyss-Coray T and Mucke L: Inflammation in neurodegenerative disease - a double-edged sword. *Neuron* 35: 419-432, 2002.
16. Lull ME and Block ML: Microglial activation and chronic neurodegeneration. *Neurotherapeutics* 7: 354-365, 2010.
17. Das Sarma J: Microglia-mediated neuroinflammation is an amplifier of virus-induced neuropathology. *J Neurovirol* 20: 122-136, 2014.
18. Glass CK, Saijo K, Winner B, Marchetto MC and Gage FH: Mechanisms underlying inflammation in neurodegeneration. *Cell* 140: 918-934, 2010.

19. Teeling JL and Perry VH: Systemic infection and inflammation in acute CNS injury and chronic neurodegeneration: Underlying mechanisms. *Neuroscience* 158: 1062-1073, 2009.
20. Taylor JP, Hardy J and Fischbeck KH: Toxic proteins in neurodegenerative disease. *Science* 296: 1991-1995, 2002.
21. Chevalier-Larsen E and Holzbaur EL: Axonal transport and neurodegenerative disease. *Biochim Biophys Acta* 1762: 1094-1108, 2006.
22. Chen H and Chan DC: Mitochondrial dynamics - fusion, fission, movement, and mitophagy - in neurodegenerative diseases. *Hum Mol Genet* 18 (R2): R169-R176, 2009.
23. Allison DJ and Ditor DS: The common inflammatory etiology of depression and cognitive impairment: A therapeutic target. *J Neuroinflammation* 11: 151, 2014.
24. de Leeuw FE, de Groot JC, Oudkerk M, Witteman JC, Hofman A, van Gijn J and Breteler MM: Hypertension and cerebral white matter lesions in a prospective cohort study. *Brain* 125: 765-772, 2002.
25. Schiffrin EL: Inflammation, immunity and development of essential hypertension. *J Hypertens* 32: 228-229, 2014.
26. Shimizu M, Ishikawa J, Yano Y, Hoshida S, Shimada K and Kario K: The relationship between the morning blood pressure surge and low-grade inflammation on silent cerebral infarct and clinical stroke events. *Atherosclerosis* 219: 316-321, 2011.
27. Tousoulis D, Kampoli AM, Papageorgiou N, Androulakis E, Antoniadou C, Toutouzas K and Stefanadis C: Pathophysiology of atherosclerosis: The role of inflammation. *Curr Pharm Des* 17: 4089-4110, 2011.
28. Di Napoli M, Godoy DA, Campi V, Masotti L, Smith CJ, Parry Jones AR, Hopkins SJ, Slevin M, Papa F, Mogoanta L, *et al*: C-reactive protein in intracerebral hemorrhage: Time course, tissue localization, and prognosis. *Neurology* 79: 690-699, 2012.
29. Di Napoli M, Parry-Jones AR, Smith CJ, Hopkins SJ, Slevin M, Masotti L, Campi V, Singh P, Papa F, Popa-Wagner A, *et al*: C-reactive protein predicts hematoma growth in intracerebral hemorrhage. *Stroke* 45: 59-65, 2014.
30. Rizzo M, Corrado E, Coppola G, Muratori I, Mezzani A, Novo G and Novo S: The predictive role of C-reactive protein in patients with hypertension and subclinical atherosclerosis. *Intern Med J* 39: 539-545, 2009.
31. Rizzo M, Corrado E, Coppola G, Muratori I, Novo G and Novo S: Markers of inflammation are strong predictors of subclinical and clinical atherosclerosis in women with hypertension. *Coron Artery Dis* 20: 15-20, 2009.
32. Goossens GH: The role of adipose tissue dysfunction in the pathogenesis of obesity-related insulin resistance. *Physiol Behav* 94: 206-218, 2008.
33. Goossens GH, Bizzarri A, Venteclef N, Essers Y, Cleutjens JP, Konings E, Jocken JW, Čajlaković M, Ribitsch V, Clément K, *et al*: Increased adipose tissue oxygen tension in obese compared with lean men is accompanied by insulin resistance, impaired adipose tissue capillarization, and inflammation. *Circulation* 124: 67-76, 2011.
34. Howcroft TK, Campisi J, Louis GB, Smith MT, Wise B, Wyss-Coray T, Augustine AD, McElhaney JE, Kohanski R and Sierra F: The role of inflammation in age-related disease. *Aging (Albany NY)* 5: 84-93, 2013.
35. Olefsky JM and Glass CK: Macrophages, inflammation, and insulin resistance. *Annu Rev Physiol* 72: 219-246, 2010.
36. Bruunsgaard H, Pedersen M and Pedersen BK: Aging and proinflammatory cytokines. *Curr Opin Hematol* 8: 131-136, 2001.
37. Fagiolo U, Cossarizza A, Santacaterina S, Ortolani C, Monti D, Paganelli R and Franceschi C: Increased cytokine production by peripheral blood mononuclear cells from healthy elderly people. *Ann N Y Acad Sci* 663: 490-493, 1992.
38. Fagiolo U, Amadori A, Cozzi E, Bendo R, Lama M, Douglas A and Palù G: Humoral and cellular immune response to influenza virus vaccination in aged humans. *Aging (Milano)* 5: 451-458, 1993.
39. Fagiolo U, Cossarizza A, Scala E, Fanales-Belasio E, Ortolani C, Cozzi E, Monti D, Franceschi C and Paganelli R: Increased cytokine production in mononuclear cells of healthy elderly people. *Eur J Immunol* 23: 2375-2378, 1993.
40. Johnson FA, Dawson AJ and Meyer RL: Activity-dependent refinement in the goldfish retinotectal system is mediated by the dynamic regulation of processes withdrawal: An in vivo imaging study. *J Comp Neurol* 406: 548-562, 1999.
41. Capuron L, Su S, Miller AH, Bremner JD, Goldberg J, Vogt GJ, Maisano C, Jones L, Murrah NV and Vaccarino V: Depressive symptoms and metabolic syndrome: Is inflammation the underlying link? *Biol Psychiatry* 64: 896-900, 2008.
42. Ouchi N, Parker JL, Lugus JJ and Walsh K: Adipokines in inflammation and metabolic disease. *Nat Rev Immunol* 11: 85-97, 2011.
43. Capuron L, Poitou C, Machaux-Tholliet D, Frochot V, Bouillot JL, Basdevant A, Layé S and Clément K: Relationship between adiposity, emotional status and eating behaviour in obese women: Role of inflammation. *Psychol Med* 41: 1517-1528, 2011.
44. Cancellaro R, Henegar C, Viguerie N, Taleb S, Poitou C, Rouault C, Coupaye M, Pelloux V, Hugol D, Bouillot JL, *et al*: Reduction of macrophage infiltration and chemoattractant gene expression changes in white adipose tissue of morbidly obese subjects after surgery-induced weight loss. *Diabetes* 54: 2277-2286, 2005.
45. McCrimmon RJ, Ryan CM and Frier BM: Diabetes and cognitive dysfunction. *Lancet* 379: 2291-2299, 2012.
46. McIntyre RS, Soczynska JK, Konarski JZ, Woldeyohannes HO, Law CW, Miranda A, Fulgosi D and Kennedy SH: Should depressive syndromes be reclassified as 'metabolic syndrome type II'? *Ann Clin Psychiatry* 19: 257-264, 2007.
47. Wolkowitz OM, Epel ES, Reus VI and Mellon SH: Depression gets old fast: Do stress and depression accelerate cell aging? *Depress Anxiety* 27: 327-338, 2010.
48. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, *et al*: Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: A STAR*D report. *Am J Psychiatry* 163: 1905-1917, 2006.
49. Baune BT, Smith E, Reppermund S, Air T, Samaras K, Lux O, Brodaty H, Sachdev P and Trollor JN: Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: The prospective Sydney Memory and Aging Study. *Psychoneuroendocrinology* 37: 1521-1530, 2012.
50. Najjar S, Pearlman DM, Devinsky O, Najjar A and Zagzag D: Neurovascular unit dysfunction with blood-brain barrier hyperpermeability contributes to major depressive disorder: A review of clinical and experimental evidence. *J Neuroinflammation* 10: 142, 2013.
51. Zunszain PA, Hepgul N and Pariante CM: Inflammation and depression. *Curr Top Behav Neurosci* 14: 135-151, 2013.
52. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR and Walters EE: Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 62: 593-602, 2005.
53. Papakostas GI, Shelton RC, Kinrys G, Henry ME, Bakow BR, Lipkin SH, Pi B, Thurmond L and Bilello JA: Assessment of a multi-assay, serum-based biological diagnostic test for major depressive disorder: A pilot and replication study. *Mol Psychiatry* 18: 332-339, 2013.
54. Rivest S: Regulation of innate immune responses in the brain. *Nat Rev Immunol* 9: 429-439, 2009.
55. Yang WX, Terasaki T, Shiroki K, Ohka S, Aoki J, Tanabe S, Nomura T, Terada E, Sugiyama Y and Nomoto A: Efficient delivery of circulating poliovirus to the central nervous system independently of poliovirus receptor. *Virology* 229: 421-428, 1997.
56. Aronsson F, Robertson B, Ljunggren HG and Kristensson K: Invasion and persistence of the neuroadapted influenza virus A/WSN/33 in the mouse olfactory system. *Viral Immunol* 16: 415-423, 2003.
57. Schnell G, Joseph S, Spudich S, Price RW and Swanson R: HIV-1 replication in the central nervous system occurs in two distinct cell types. *PLoS Pathog* 7: e1002286, 2011.
58. Chen L, Liu J, Xu C, Keblesh J, Zang W and Xiong H: HIV-1gp120 induces neuronal apoptosis through enhancement of 4-aminopyridine-sensitive outward K⁺ currents. *PLoS One* 6: e25994, 2011.
59. Chang JR, Mukerjee R, Bagashev A, Del Valle L, Chabrashvili T, Hawkins BJ, He JJ and Sawaya BE: HIV-1 Tat protein promotes neuronal dysfunction through disruption of microRNAs. *J Biol Chem* 288: 8564, 2013.
60. Brew BJ, Crowe SM, Landay A, Cysique LA and Guillemin G: Neurodegeneration and ageing in the HAART era. *J Neuroimmune Pharmacol* 4: 163-174, 2009.
61. Noh H, Jeon J and Seo H: Systemic injection of LPS induces region-specific neuroinflammation and mitochondrial dysfunction in normal mouse brain. *Neurochem Int* 69: 35-40, 2014.

62. Zhou L, Miranda-Saksena M and Saksena NK: Viruses and neurodegeneration. *Virology* 10: 172, 2013.
63. Ostanin DV, Bao J, Koboziev I, Gray L, Robinson-Jackson SA, Kosloski-Davidson M, Price VH and Grisham MB: T cell transfer model of chronic colitis: Concepts, considerations, and tricks of the trade. *Am J Physiol Gastrointest Liver Physiol* 296: G135-G146, 2009.
64. Huber S, Schramm C, Lehr HA, Mann A, Schmitt S, Becker C, Protschka M, Galle PR, Neurath MF and Blessing M: Cutting edge: TGF- β signaling is required for the in vivo expansion and immunosuppressive capacity of regulatory CD4+CD25+ T cells. *J Immunol* 173: 6526-6531, 2004.
65. Martinez FO and Gordon S: The M1 and M2 paradigm of macrophage activation: time for reassessment. *F1000Prime Rep* 6: 13, 2014.
66. Crutcher KA, Gendelman HE, Kipnis J, Perez-Polo JR, Perry VH, Popovich PG and Weaver LC: Debate: 'is increasing neuroinflammation beneficial for neural repair?'. *J Neuroimmune Pharmacol* 1: 195-211, 2006.
67. Popovich PG and Longbrake EE: Can the immune system be harnessed to repair the CNS? *Nat Rev Neurosci* 9: 481-493, 2008.
68. Tansey MG, McCoy MK and Frank-Cannon TC: Neuroinflammatory mechanisms in Parkinson's disease: Potential environmental triggers, pathways, and targets for early therapeutic intervention. *Exp Neurol* 208: 1-25, 2007.
69. Schmid CD, Melchior B, Masek K, Puntambekar SS, Danielson PE, Lo DD, Sutcliffe JG and Carson MJ: Differential gene expression in LPS/IFN γ activated microglia and macrophages: In vitro versus in vivo. *J Neurochem* 109 (Suppl 1): 117-125, 2009.
70. Block ML and Hong JS: Microglia and inflammation-mediated neurodegeneration: Multiple triggers with a common mechanism. *Prog Neurobiol* 76: 77-98, 2005.
71. González H, Elgueta D, Montoya A and Pacheco R: Neuroimmune regulation of microglial activity involved in neuroinflammation and neurodegenerative diseases. *J Neuroimmunol* 274: 1-13, 2014.
72. Henkel JS, Engelhardt JI, Siklós L, Simpson EP, Kim SH, Pan T, Goodman JC, Siddique T, Beers DR and Appel SH: Presence of dendritic cells, MCP-1, and activated microglia/macrophages in amyotrophic lateral sclerosis spinal cord tissue. *Ann Neurol* 55: 221-235, 2004.
73. Mrak RE and Griffin WST: Glia and their cytokines in progression of neurodegeneration. *Neurobiol Aging* 26: 349-354, 2005.
74. Rock RB, Gekker G, Hu S, Sheng WS, Cheeran M, Lokensgard JR and Peterson PK: Role of microglia in central nervous system infections. *Clin Microbiol Rev* 17: 942-964, 2004.
75. Qian L, Tan KS, Wei SJ, Wu HM, Xu Z, Wilson B, Lu RB, Hong JS and Flood PM: Microglia-mediated neurotoxicity is inhibited by morphine through an opioid receptor-independent reduction of NADPH oxidase activity. *J Immunol* 179: 1198-1209, 2007.
76. Gordon R, Anantharam V, Kanthasamy AG and Kanthasamy A: Proteolytic activation of proapoptotic kinase protein kinase C δ by tumor necrosis factor α death receptor signaling in dopaminergic neurons during neuroinflammation. *J Neuroinflammation* 9: 82, 2012.
77. Magro F, Fraga S, Ribeiro T and Soares-da-Silva P: Decreased availability of intestinal dopamine in transmural colitis may relate to inhibitory effects of interferon- γ upon L-DOPA uptake. *Acta Physiol Scand* 180: 379-386, 2004.
78. Panaro MA, Lofrumento DD, Saponaro C, De Nuccio F, Cianciulli A, Mitolo V and Nicolardi G: Expression of TLR4 and CD14 in the central nervous system (CNS) in a MPTP mouse model of Parkinson's-like disease. *Immunopharmacol Immunotoxicol* 30: 729-740, 2008.
79. Querfurth HW and LaFerla FM: Alzheimer's disease. *N Engl J Med* 362: 329-344, 2010.
80. Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN and Braak E: Staging of brain pathology related to sporadic Parkinson's disease. *Neurobiol Aging* 24: 197-211, 2003.
81. Saccon RA, Bunton-Stasyshyn RK, Fisher EM and Fratta P: Is SOD1 loss of function involved in amyotrophic lateral sclerosis? *Brain* 136: 2342-2358, 2013.
82. Lu L, Lan Q, Li Z, Zhou X, Gu J, Li Q, Wang J, Chen M, Liu Y, Shen Y, *et al*: Critical role of all-trans retinoic acid in stabilizing human natural regulatory T cells under inflammatory conditions. *Proc Natl Acad Sci USA* 111: E3432-E3440, 2014.
83. Appel SH: CD4+ T cells mediate cytotoxicity in neurodegenerative diseases. *J Clin Invest* 119: 13-15, 2009.
84. Reynolds AD, Stone DK, Mosley RL and Gendelman HE: Proteomic studies of nitrated alpha-synuclein microglia regulation by CD4+CD25+ T cells. *J Proteome Res* 8: 3497-3511, 2009.