IL-10 in Neurodegenerative Diseases

Subjects: Biochemistry & Molecular Biology

Contributor: Maria Antonietta Panaro

IL-10, an immunosuppressive cytokine, is considered an important anti-inflammatory modulator of glial activation, preventing inflammation-mediated neuronal degeneration under pathological conditions. In this narrative review, we summarize recent insights about the role of IL-10 in the neurodegeneration associated with neuroinflammation, in diseases such as Multiple Sclerosis, Traumatic Brain Injury, Amyotrophic lateral sclerosis, Alzheimer's Disease, and Parkinson's Disease, focusing on the contribution of this cytokine not only in terms of protective action, but also as possibly responsible for clinical worsening. The knowledge of this double face of the same coin, regarding the biological role of the IL-10, could aid the development of targeted therapies useful for limiting neurodegenerative processes.

Keywords: IL-10 ; microglia ; neurodegeneration ; neuroinflammation ; signaling

1. Definition

IL-10, an immunosuppressive cytokine, is considered an important anti-inflammatory modulator of glial activation, preventing inflammation-mediated neuronal degeneration under pathological conditions.

2. Introduction

Interleukin (IL)-10, a potent anti-inflammatory cytokine, plays a critical role in balancing immune responses in order to circumvent chronic inflammatory diseases [1]. It was first described after the analysis for secreted factors by immunomodulatory CD4+ T helper 2 (Th2) mouse lymphocytes (named as anti-inflammatory cells) that can regulate CD4+ T helper 1 (Th1) lymphocytes (reported as pro-inflammatory cells) [2][3].

IL-10 acts in innate as well as in adaptive immunity, both in terms of immunosuppressive and immunostimulatory effects, thus, regulating response in many cell types, such as antigen-presenting cells (APCs), including dendritic cells (DCs), Langerhans cells, and macrophages [4].

Inflammatory responses play a central role in the pathophysiology of several neurodegenerative diseases. In this regard, neuroinflammation is characterized by the activation of resident glial cells, committed to central nervous system (CNS) immune surveillance, through the release of cytokines, chemokines, and other mediators, which, in turn, are able to recruit peripheral cells, including lymphocytes, monocytes and neutrophils [5][6].

In the course of CNS pathology, the levels of IL-10 significantly increase in the brain in order to ensure nervous tissue survival and mitigate inflammatory responses triggering several signaling pleiotropic pathways [7].

3. IL-10 in Brain Diseases

Multiple sclerosis (MS) is an immune-mediated, inflammatory disease characterized by multifocal areas of demyelination in the CNS. The exact cause of MS is not yet well clarified, but it was reported that increased cytokine levels seem to play a crucial role in its pathogenesis, although it is not clear whether it leads to a beneficial or harmful effect. Among these cytokines, TNFα, IFN-γ, IL-1, IL-6, and IL-12 resulted positively correlated to the severity and progression of MS. Apart from the aforementioned cytokines involved in pro-inflammatory effects observed in the CNS of both MS patients and in animal models, there is evidence for the presence of several other cytokines, including IL-10, actively implicated in anti-inflammatory events in an attempt to assure the axonal and myelin integrity [8].

The genetic polymorphism related to the IL-10 gene responsible for the reduced expression of this cytokine has been related to the onset of MS symptoms in patients [9]. These observations were confirmed by what was found in mouse models of experimental autoimmune encephalomyelitis (EAE), in which the increase in IL-10 levels leads to symptoms

reduction [10]. In this regard, other authors also reported that IL-10 expression in the CNS correlates to the onset of the recovery phase of EAE [11][12].

Although MS is primarily considered a T cell-mediated disease, successful B cell depletion with anti-CD20 monoclonal antibodies [13] suggests that these cells play an indispensable role in MS pathogenesis. Recently, it was also observed that B cells exhibit regulatory functions through TLR and CD40-mediated IL-10 production. In MS, TLR4- or TLR9-mediated signaling plays distinct roles in regulating IL-10 production by B lymphocytes. B cells from MS patients are deficient in their capacity to produce IL-10 after either TLR9 or CD40 stimulation, whereas TLR4-mediated IL-10 production was restored to normal levels in MS and further increased at relapse in the presence of CD40 signaling, thus, demonstrating that regulation of TLR4 and CD40 signaling in B cells may be a promising novel approach for MS therapy [14]. Consistent to this finding, previous studies reported that CD40 stimulation triggered continuous IL-10 production by human B cells in response to TLR stimulation correlating with B cell-mediated recovery from EAE by IL-10 production [15] [16], promising a novel therapeutic approach for MS.

Furthermore, the employment of reinfusion of CD40-dependent IL-10-secreting autologous functional B cells was resulted to be an innovative and efficacious in vivo treatment for severe autoimmune diseases resistant to current therapies, including MS [17].

Traumatic brain injury (TBI) is characterized by a complex devastating injury with a broad spectrum of symptoms and disabilities, in which neuroinflammation plays a crucial role, being both protective and detrimental for brain compartments.

In this context, the release of mediators causing inflammation, such as pro-inflammatory cytokines and free radicals, although mainly produced for guaranteeing nervous tissue repair, is responsible for blood–brain–barrier (BBB) damage, leading to ischemia and cerebral edema [18]. It is well documented that IL-10 levels in humans and experimental animal models resulted significantly augmented both in the serum and CSF after TBI tending to remain elevated several days later [18]. Different experimental models, both in vitro and in vivo, evidenced that in ischemic strokes, IL-10 is implicated in neuroprotective action other than being an interesting and clinically useful diagnostic tool in TBI patients [19][20][21].

Conversely, other studies reported that elevated IL-10 levels correlate with severity and mortality in severe TBI [22]. In addition, higher levels of IL-10 in CSF were significantly associated with mortality both in pediatric and in adult patients [23].

A recent study reported that transplantation of mesenchymal stem cells engineered to overexpress IL-10 can reduce inflammation, determining a favorable outcome to the injured area. This result has been explained through the shifting of macrophages from pro-inflammatory to a pro-repair phenotype, thus, emphasizing the possible employment of IL-10 overexpression as a new therapeutic strategy for TBI treatment [24].

Among neurodegenerative diseases, Amyotrophic lateral sclerosis (ALS) is characterized by a rapid loss of motor neurons, both in the brain and spinal cord, that leads to paralysis and ultimately, death, in which neuroinflammation is one of the more frequently investigated key features [25]. Recent studies conducted in an animal model of ALS evidenced a specific role for IL-10 in the early stage of disease, clearly demonstrating that this cytokine plays a crucial role in orchestrating the immune responses of microglial cells [26]. In this regard, targeted overexpression of IL-10 in microglia seems to have therapeutic potential in ALS, since IL-10, assuring a microglial neuroprotective phenotype, delays neuronal dysfunction. As confirmation of this last observation, it is noteworthy that IL-10 production becomes deregulated with aging, resulting in reactive microgliosis and neuronal stress [27].

Other observations revealed characteristic changes in the levels not only of pro-inflammatory cytokines TNF-α and IL-6, but also of the anti-inflammatory cytokine IL-10, both in the spinal cord and in the serum of mice injected intraperitoneally with the IgG from the ALS patients accompanied with subclinical signs of motoneuron diseases, thus, evidencing the importance of the delicate balance between the pro- and anti-inflammatory mechanisms in neurodegeneration such as ALS [28]. Moreover, it was reported that IL-10 levels resulted high in ALS patients exhibiting a slowly progressive course or mild symptoms, thus, suggesting a possible neuroprotective action by this cytokine [29]. Su et al. [30] showed that depending on the cytokines found in plasma of ALS patients, shorter (IL-1β and IL-12) or longer (IL-10) disease duration can be predicted, thus, suggesting that a lesser degree of inflammation might be associated with more favorable prognosis. In another study described by Ehrhart [31], no significant differences were observed in terms of anti-inflammatory IL-4 and IL-10 cytokine concentrations in ALS patients versus control subjects. Therefore, at present, there is little information regarding the exact role of IL-10 during ALS in order to reach conclusive outcomes.

In a recent study, Jin M. et al. have studied the immune profile of peripheral blood and the serum cytokine pattern of 73 ASL patients, finding that the immune profile was shifted towards a Th1/Th17 cell-mediated pro-inflammatory response. Moreover, because the serum pro-inflammatory cytokines such as IL-1β, IL-6 and IFN-γ increased, whereas the anti-inflammatory IL-10 decreased, the authors correlated these events with disease severity and progression [32].

Alzheimer's disease (AD), the most common cause of dementia in older adults, is a chronic neurodegenerative disease characterized by progressive loss of brain cells, formation of extracellular amyloid β (Aβ) plaques and intracellular neurofibrillary tangles [33]. Although the role of inflammation in AD is still uncertain, the increased expression of inflammatory mediators in the brains of AD patients and several epidemiological studies evidence a link between the use of anti-inflammatory drugs and the course of disease.

Pro- and anti-inflammatory cytokines are both decisive for the Aβ plaques' onset in the brains of AD patients. In the aging brain, a combination of cytokines, such as IL-1β, IL-6, IL-8, IL-10, IL-12 and TNFα, is reported to trigger inflammatory processes associated with cortical atrophy [34].

To evaluate cerebral inflammation in AD, amnestic Mild Cognitive Impairment (aMCI) patients and aged matched healthy volunteers, Cisbani G et al. used radioligands targeting TSPO, a translocator protein strongly expressed in microglia and macrophages during inflammation, in conjunction with positron emission tomography (PET) imaging. Analyzing the association between candidate peripheral biomarkers (including amyloid beta, cytokines and serum total fatty acids) with brain TSPO levels, they found that serum IL-6 and IL-10 are higher in AD compared to the aMCI and healthy volunteers, whereas serum amyloid beta, cytokines and fatty acids were generally not correlated with neuroinflammation [35].

Moreover, apart from evidence reporting that IL-1 β is the most important pro-inflammatory cytokine contributing to an increased AD incidence, a weak expression of anti-inflammatory cytokines, including IL-10, exposes the subjects to a greater susceptibility to develop disease [30]. In this regard, IL-10 overexpression in the hippocampus of AD transgenic mice has been reported to increase neurogenesis and enhance cognition, thus, evidencing the probable neuroprotective role played by IL-10 in this pathological condition [36].

Conversely, other studies seem to support a detrimental effect by IL-10 causing Aβ clearance, inhibition in microglia, and worsening cognitive decline in AD mouse models [37]. IL-10 genetic ablation in APP/PS1 mice led to significant decline of the area interested by Aβ plaques' presence, both in the cortex and hippocampus. In addition, it was observed that the severity of cerebral amyloid angiopathy, characterized by the deposition of Aβ within the blood vessels walls, was also reduced in this animal model [38]. On the other hand, a recent study [39] reported that promoter haplotypes of IL-10 may be important modulators of the development of amnestic mild cognitive impairment, thus, confirming previous observations regarding the linkage of polymorphisms in the promoter region of IL-10 and risk factors of AD [40].

Parkinson's disease (PD) is a progressive nervous system disorder due to nigrostriatal dopamine neurons loss and is characterized by several clinical features, including bradykinesia, rigidity, tremor, and postural instability. Neuroinflammation is an important risk factor that may contribute to PD pathogenesis, since PD patients suffer from chronic inflammation that probably precedes neurodegeneration and cytokines produced by activated microglia in the substantia nigra (SN) and putamen in the course of PD [41].

It was observed in the brains in the LPS-induced PD mouse model that IL-10 decreased the number of activated microglia with a protective effect regarding the loss of dopaminergic neuron [42]. Moreover, PD patients with more severe clinical signs and a prognostically unfavorable non-tremor form show drastically reduced serum levels of IL-10 [43]. Alternatively, high plasma IL-10 levels have been detected in PD patients with classical motor symptoms in comparison to healthy controls [44]. However, in another study, it was reported that IL-10 levels seem not to be correlated to non-motor symptoms [45]. In addition, Li et al. detected both elevated levels of IL-1β and depressed levels of IL-10 in the peripheral blood of patients with PD-related pain, thus, suggesting the implication of several inflammatory cytokines, including IL-10, in the occurrence of PD-related pain [46].

Various studies have investigated a possible correlation between IL-10 polymorphisms and potential risk of PD onset. In this regard, some observations evidenced no association [47][48], although other studies showed that IL-10 promoter polymorphisms−819 and −1082 seem to be associated with PD risk and early PD occurrence [49].

A recent report showed increased peripheral concentrations of IL-6, IL-1β, TNFα, IL-2 and IL-10 in patients with PD [50]. Similarly, in the analyses of newly diagnosed PD patients, IL-1β, TNFα, IL-2 and IL-10 resulted elevated [51]. Although IL-10 generally has effects able to oppose the actions of the pro-inflammatory cytokines, its bioactivity is highly complex in

the immunoregulation, including both immunosuppressive as well as immunostimulatory activities, as previously reported [1].

Interestingly, a correlation between IL-10 levels and gastrointestinal symptoms in the early stage of PD was also recently reported, thus, reflecting a protective response against inflammatory processes associated with the disease [52].

These observations suggest not only that certain inflammatory cytokines may be implicated in the occurrence and clinical symptoms of PD, but also that IL-10 may constitute a potential target for the development of new drugs.

References

1. Mosser, D.M.; Zhang, X. Interleukin-10: New perspectives on an old cytokine. Immunol. Rev. 2008, 226, 205–218.
2. Fiorentino, D.F.; Bond, M.W.; Mosmann, T.R. Two types of mouse T helper cell. IV. Th2 clones secrete a factor that inhi bits cytokine production by Th1 clones. J. Exp. Med. 1989, 170, 2081–2095.
3. Moore, K.W.; Vieira, P.; Fiorentino, D.F.; Trounstine, M.L.; Khan, T.A.; Mosmann, T.R. Homology of cytokine synthesis i nhibitory factor (IL-10) to the Epstein-Barr virus gene BCRFI. Science 1990, 248, 1230–1234.
4. Roncarolo, M.G.; Gregori, S.; Battaglia, M.; Bacchetta, R.; Fleischhauer, K.; Levings, M.K. Interleukin-10-secreting type 1 regulatory T cells in rodents and humans. Immunol. Rev. 2006, 212, 28–50.
5. Patterson, Z.R.; Holahan, M.R. Understanding the neuroinflammatory response following concussion to develop treatm ent strategies. Front. Cell. Neurosci. 2012, 6, 58.
6. Ziebell, J.M.; Morganti-Kossmann, M.C. Involvement of pro- and anti-inflammatory cytokines and chemokines in the pat hophysiology of traumatic brain injury. Neurotherapeutics 2010, 7, 22–30.
7. Strle, K.; Zhou, J.H.; Broussard, S.R.; Venters, H.D.; Johnson, R.W.; Freund, G.G.; Dantzer, R.; Kelley, K.W. IL-10 pro motes survival of microglia without activating Akt. J. Neuroimmunol. 2002, 122, 9–19.
8. Martinez Doncel, A.; Rubio, A.; Arroyo, R.; de las Heras, V.V.; Martín, C.; Fernandez-Arquero, M.; de la Conchaa, E.G. I nterleukin-10 polymorphisms in spanish multiple sclerosis patients. J. Neuroimmunol. 2002, 131, 168–172.
9. Myhr, K.M.; Vågnes, K.S.; Marøy, T.H.; Aarseth, J.H.; Nyland, H.I.; Vedeler, C.A. Interleukin-10 promoter polymorphism s in patients with multiple sclerosis. J. Neurol. Sci. 2002, 202, 93–97.
10. O'Neill, E.J.; Day, M.J.; Wraith, D.C. IL-10 is essential for disease protection following intranasal peptide administration in the C57BL/6 model of EAE. J. Neuroimmunol. 2006, 178, 1–8.
11. Klose, J.; Schmidt, N.O.; Melms, A.; Dohi, M.; Miyazaki, J.; Bischof, F.; Greve, B. Suppression of experimental autoimm une encephalomyelitis by interleukin-10 transduced neural stem/progenitor cells. J. Neuroinflamm. 2013, 10, 17.
12. Yen, J.H.; Xu, S.; Park, Y.S.; Ganea, D.; Kim, K.C. Higher susceptibility to experimental autoimmune encephalomyelitis in Muc1-deficient mice is associated with increased Th1/Th17 responses. Brain Behav. Immun. 2013, 29, 70–81.
13. Hauser, S.L.; Waubant, E.; Arnold, D.L.; Vollmer, T.; Antel, J.; Fox, R.J.; Bar-Or, A.; Panzara, M.; Sarkar, N.; Agarwal, S.; et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N. Engl. J. Med. 2008, 358, 676–688.
14. Okada, Y.; Ochi, H.; Fujii, C.; Hashi, Y.; Hamatani, M.; Ashida, S.; Kawamura, K.; Kusaka, H.; Matsumoto, S.; Nakagaw a, M.; et al. Signaling via toll-like receptor 4 and CD40 in B cells plays a regulatory role in the pathogenesis of multiple sclerosis through interleukin-10 production. J. Autoimmun. 2018, 88, 103–113.
15. Lampropoulou, V.; Hoehlig, K.; Roch, T.; Neves, P.; Calderón Gómez, E.; Sweenie, C.H.; Hao, Y.; Freitas, A.A.; Steinhof f, U.; Anderton, S.M.; et al. TLR-activated B cells suppress T cell-mediated autoimmunity. J. Immunol. 2008, 180, 4763 –4773.
16. Korniotis, S.; Gras, C.; Letscher, H.; Montandon, R.; Mégret, J.; Siegert, S.; Ezine, S.; Fallon, P.G.; Luther, S.A.; Fillatre au, S.; et al. Treatment of ongoing autoimmune encephalomyelitis with activated B-cell progenitors maturing into regula tory B cells. Nat. Commun. 2016, 7, 12134.
17. Yoshizaki, A.; Miyagaki, T.; DiLillo, D.J.; Matsushita, T.; Horikawa, M.; Kountikov, E.I.; Spolski, R.; Poe, J.C.; Leonard, W.J.; Tedder, T.F. Regulatory B cells control T-cell autoimmunity through IL-21-dependent cognate interactions. Nature 2012, 491, 264–268.
18. Garcia, J.M.; Stillings, S.A.; Leclerc, J.L.; Phillips, H.; Edwards, N.J.; Robicsek, S.A.; Hoh, B.L.; Blackburn, S.; Sylvain Doré, S. Role of interleukin-10 in acute brain injuries. Front. Neurol. 2017, 8, 244.
19. Woodcock, T.; Morganti-Kossmann, M.C. The role of markers of inflammation in traumatic brain injury. Front. Neurol. 20 13, 4, 18.

20. Li, Z.; Zeng, G.; Zheng, X.; Wang, W.; Ling, Y.; Tang, H.; Zhang, J. Neuroprotective effect of formononetin against TBI i n rats via suppressing inflammatory reaction in cortical neurons. Biomed. Pharmacother. 2018, 106, 349–354.

21. Lagerstedt, L.; Egea-Guerrero, J.J.; Rodríguez-Rodríguez, A.; Bustamante, A.; Montaner, J.; El Rahal, A.; Andereggen, E.; Rinaldi, L.; Sarrafzadeh, A.; Schaller, K.; et al. Early measurement of interleukin-10 predicts the absence of CT scan lesions in mild traumatic brain injury. PLoS ONE 2018, 13, e0193278.

22. Schneider Soares, M.; Menezes de Souza, N.; Liborio Schwarzbold, M.; Paim Diaz, A.; Costa Nunes, J.; Hohl, A.; Wal z, R. Interleukin-10 is an independent biomarker of severe traumatic brain injury prognosis. Neuroimmunomodulation 2 012, 19, 377–385.

23. Kirchhoff, C.; Buhmann, S.; Bogner, V.; Stegmaier, J.; Leidel, B.A.; Braunstein, V.; Mutschler, W.; Biberthaler, P. Cerebr ospinal IL-10 concentration is elevated in non-survivors as compared to survivors after severe traumatic brain injury. Eu r. J. Med. Res. 2008, 13, 464–468.

24. Peruzzaro, S.T.; Andrews, M.M.M.; Al-Gharaibeh, A.; Pupiec, O.; Resk, M.; Story, D.; Maiti, P.; Rossignol, J.; Dunbar, G.L. Transplantation of mesenchymal stem cells genetically engineered to overexpress interleukin-10 promotes alternat ive inflammatory response in rat model of traumatic brain injury. J. Neuroinflamm. 2019, 16, 2.

25. Kim, R.B.; Irvin, C.W.; Tilva, K.R.; Mitchell, C.S. State of the field: Aninformatics-based systematic review of the SOD1-G93A Amyotrophic Lateral Sclerosis transgenic mouse model. Amyotroph. Lateral Scler. Front. Degener. 2015, 17, 1–1 4.

26. Gravel, M.; Béland, L.C.; Soucy, G.; Abdelhamid, E.; Rahimian, R.; Gravel, C.; Kriz, J. IL-10 controls early microglial ph enotypes and disease onset in als caused by misfolded superoxide dismutase 1. J. Neurosci. 2016, 36, 1031–1048.

27. Ciaramella, A.; Spalletta, G.; Bizzoni, F.; Salani, F.; Caltagirone, C.; Bossù, P. Effect of age on surface molecules and c ytokine expression in human dendritic cells. Cell. Immunol. 2011, 269, 82–89.

28. Obál, I.; Klausz, G.; Mándi, Y.; Deli, M.; Siklós, L.; Engelhardt, J.I. Intraperitoneally administered IgG from patients with amyotrophic lateral sclerosis or from an immune-mediated goat model increase the levels of TNF-α, IL-6, and IL-10 in t he spinal cord and serum of mice. J. Neuroinflamm. 2016, 13, 121.

29. Furukawa, T.; Matsui, N.; Fujita, K.; Nodera, H.; Shimizu, F.; Miyamoto, K.; Takahashi, Y.; Kanda, T.; Kusunoki, S.; Izum i, Y.; et al. CSF cytokine profile distinguishes multifocal motor neuropathy from progressive muscular atrophy. Neurol. N euroimmunol. Neuroinflamm. 2015, 2, e138.

30. Su, F.; Bai, F.; Zhang, Z. Inflammatory cytokines and Alzheimer's disease: A review from the perspective of genetic poly morphisms. Neurosci. Bull. 2016, 32, 469–480.

31. Ehrhart, J.; Smith, A.J.; Kuzmin-Nichols, N.; Zesiewicz, T.A.; Jahan, I.; Shytle, R.D.; Kim, S.-H.; Sanberg, C.D.; Vu, T. H.; Gooch, C.L.; et al. Humoral factors in ALS patients during disease progression. J. Neuroinflamm. 2015, 12, 127.

32. Jin, M.; Günther, R.; Akgün, K.; Hermann, A.; Ziemssen, T. Peripheral proinflammatory Th1/Th17 immune cell shift is lin ked to disease severity in amyotrophic lateral sclerosis. Sci. Rep. 2020, 10, 1–13.

33. Long, J.M.; Holtzman, D.M. Alzheimer disease: An update on pathobiology and treatment strategies. Cell 2019, 179, 31 2–339.

34. Cisbani, G.; Koppel, A.; Knezevic, D.; Suridjan, I.; Mizrahi, R.; Bazinet, R.P. Peripheral cytokine and fatty acid associati ons with neuroinflammation in AD and AMCI Patients: An exploratory study. Brain Behav. Immun. 2020, 87, 679–688.

35. Baune, B.T.; Ponath, G.; Rothermundt, M.; Roesler, A.; Berger, K. Association between cytokines and cerebral MRI cha nges in the aging brain. J. Geriatr. Psychiatry Neurol. 2009, 22, 23–34.

36. Kiyota, T.; Ingraham, K.L.; Swan, R.J.; Jacobsen, M.T.; Andrews, S.J.; Ikezu, T. AAV serotype 2/1-mediated gene delive ry of anti-inflammatory interleukin-10 enhances neurogenesis and cognitive function in APP+PS1 mice. Gene Ther. 201 2, 19, 724–733.

37. Michaud, J.P.; Rivest, S. Anti-inflammatory signaling in microglia exacerbates Alzheimer's disease-related pathology. N euron 2015, 85, 450–452.

38. Guillot-Sestier, M.V.; Doty, K.R.; Gate, D.; Rodriguez, J., Jr.; Leung, B.P.; Rezai-Zadeh, K.; Town, T. Il10 deficiency reba lances innate immunity to mitigate Alzheimer-like pathology. Neuron 2015, 85, 534–548.

39. Bai, F.; Xie, C.; Yuan, Y.; Shi, Y.; Zhang, Z. Promoter haplotypes of interleukin-10 gene linked to cortex plasticity in subj ects with risk of Alzheimer's disease. Neuroimage Clin. 2017, 17, 587–595.

40. Mun, M.J.; Kim, J.H.; Choi, J.Y.; Jang, W.C. Genetic polymorphisms of interleukin genes and the risk of Alzheimer's dis ease: An update meta-analysis. Meta Gene 2016, 8, 1–10.

41. Panaro, M.A.; Cianciulli, A. Current opinions and perspectives on the role of immune system in the pathogenesis of Par kinson's disease. Curr. Pharm. Des. 2012, 18, 200–208.

42. Kwilasz, A.J.; Grace, P.M.; Serbedzija, P.; Maier, S.F.; Watkins, L.R. The therapeutic potential of interleukin-10 in neuroi mmune diseases. Neuropharmacology 2015, 96, 55–69.
43. Karpenko, M.N.; Vasilishina, A.A.; Gromova, E.A.; Muruzheva, Z.M.; Bernadotte, A. Interleukin-1β, interleukin-1 recepto r antagonist, interleukin-6, interleukin-10, and tumor necrosis factor-α levels in CSF and serum in relation to the clinical diversity of Parkinson’s disease. Cell. Immunol. 2018, 327, 77–82.
44. Rentzos, M.; Nikolaou, C.; Andreadou, E.; Paraskevas, G.P.; Rombos, A.; Zoga, M.; Tsoutsou, A.; Boufidou, F.; Kapaki, E.; Vassilopoulos, D. Circulating interleukin-10 and interleukin-12 in Parkinson’s disease. Acta Neurol. Scand. 2009, 11 9, 332–337.
45. Menza, M.; Dobkin, R.D.; Marin, H.; Mark, M.H.; Gara, M.; Bienfait, K.; Dicke, A.; Kusnekov, A. The role of inflammatory cytokines in cognition and other non-motor symptoms of Parkinson’s disease. Psychosomatics 2010, 51, 474–479.
46. Li, D.; Song, X.; Huang, H.; Huang, H.; Ye, Z. Association of Parkinson’s disease-related pain with plasma interleukin-1, interleukin-6, interleukin-10, and tumour necrosis factor-α. Neurosci. Lett. 2018, 683, 181–184.
47. Chu, K.; Zhou, X.; Luo, B.Y. Cytokine gene polymorphisms and Parkinson’s disease: A meta-analysis. Can. J. Neurol. S ci. 2012, 39, 58–64.
48. Pascale, E.; Passarelli, E.; Purcaro, C.; Vestri, A.R.; Fakeri, A.; Guglielmi, R.; Passarelli, F.; Meco, G. Lack of associatio n between IL-1beta, TNF-alpha, and IL-10 gene polymorphisms and sporadic Parkinson’s disease in an Italian cohort. Acta Neurol. Scand. 2011, 124, 176–181.
49. Li, D.; He, Q.; Li, R.; Xu, X.; Chen, B.; Xie, A. Interleukin-10 promoter polymorphisms in Chinese patients with Parkinso n’s disease. Neurosci. Lett. 2012, 513, 183–186.
50. Qin, X.Y.; Zhang, S.P.; Cao, C.; Loh, Y.P.; Cheng, Y. Aberrations in peripheral inflammatory cytokine levels in Parkinson disease: A systematic review and meta-analysis. JAMA Neurol. 2016, 73, 1316–1324.
51. Williams-Gray, C.H.; Wijeyekoon, R.; Yarnall, A.J.; Lawson, R.A.; Breen, D.P.; Evans, J.R.; Cummins, G.A.; Duncan, G. W.; Khoo, T.K.; Burn, D.J.; et al. Serum immune markers and disease progression in an incident Parkinson’s disease c ohort (ICICLE-PD). Mov. Disord. 2016, 31, 995–1003.
52. Kim, R.; Kim, H.J.; Kim, A.; Jang, M.; Kim, A.; Kim, Y.; Yoo, D.; Im, J.H.; Choi, J.H.; Jeon, B. Peripheral blood inflammat ory markers in early Parkinson’s disease. J. Clin. Neurosci. 2018, 58, 30–33.