We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

6,300

Open access books available

172,000

International authors and editors

190M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities

WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com

Toll-Like Receptors (TLRs) in Neurodegeneration: Integrative Approach to TLR Cascades in Alzheimer's and Parkinson's Diseases

Juan M. Zolezzi, Sussy Bastías-Candia and Nibaldo C. Inestrosa

Abstract

Sterile inflammatory response constitutes a main event in several neurodegenerative disorders. Alzheimer's disease (AD) and Parkinson's disease (PD), the leading degenerative pathologies of the central nervous system worldwide, exhibit a strong inflammatory component. Microglial and astrocytic reactivity, increased levels of inflammatory mediators, neuronal damage, and death are part of the pathological scenario leading to the progressive failure of the brain neuronal network. In this regard, the link between the toll-like receptors (TLRs)-mediated inflammatory cascade and the molecular hallmarks of AD and PD have been demonstrated elsewhere. Moreover, the long-lasting exposure to the inflammatory environment is considered one of the key elements leading to the establishment and progression of these pathologies. Accordingly, the modulation of the inflammatory response has emerged as a main target of new therapeutic approaches to fight these diseases. In this regard, and based on our previous works on this subject, we describe the pathological profile of both pathologies but in the inflammatory context. Thus, in the present chapter, we will introduce the main aspects of both diseases and how they interplay with the TLR-mediated response. We believe that this chapter should provide a concise overview of the roles of TLRs in the inflammatory cascades triggered during AD and PD pathophysiology.

Keywords: neurodegeneration, neuroinflammatory response, toll-like receptors, Alzheimer's disease, Parkinson's disease

1. Introduction

The aging of the world population has been demonstrated systematically by several demographic studies. Regrettably, increased life expectancy has led to an increased prevalence of age-related disorders including neurodegenerative diseases. In this regard, Alzheimer's and Parkinson's diseases constitute the most relevant issues for the public health system of different countries. Accordingly, during the last decades, significant efforts have been committed to improve our understanding of the molecular cascades responsible for an altered aging process as well as for the

establishment and progression of neurodegenerative disorders, mainly Alzheimer's disease (AD) and Parkinson's disease (PD) [1].

Relevantly, though AD and PD possess their very own pathological characteristics, the neuroinflammatory milieu has emerged as a central event of the chronic degenerative process. From the prodromal stage of these disorders up to the more advanced ones, inflammation seems to accompany or, in some cases, to drive the progression of AD and PD. Importantly, inflammation, as part of the nonspecific immune response, plays a critical role in maintenance of system homeostasis, allowing to prevent or to control the detrimental effects induced by a wide variety of xenobiotics to the cellular components of the biological systems. Remarkably, from an unspecific harmful stimulus, a whole range of responses are triggered including complement cascade activation and cytokines release as well as activation of the immune cells located at the site of the insult. To properly eliminate the initial cause of distress and to repair the damaged tissue, the inflammatory response must be delicately balanced considering not only pro-inflammatory but anti-inflammatory mediators as well. Tumor necrosis factor 1 (TNF-1 α), interleukins (IL-1, IL-8, IL-10), interferon (INF- γ), transforming growth factor 1 (TGF-1), complement proteins, act together to develop a coordinated response against primary, unspecific stimuli [2, 3]. In this regard, the compromise of this essential system relates with severe, and often lethal, conditions including immunodeficiency syndromes as well as autoimmune diseases. Relevantly, during the last decades, a lot of attention has been also given to the effects of chronic inflammatory condition as the starting point of different degenerative conditions. Among these, neurodegenerative disorders, such as Alzheimer's and Parkinson's diseases, have found in the inflammatory response a critical milieu of events able to determinate the main molecular and cellular events verified during each of these diseases [4].

2. Central nervous system (CNS) immunocompetence

CNS is a highly specialized structure whose functions require specific microenvironmental conditions. Moreover, neuronal activity and, thus, the health of the neuronal network depend on the maintenance of ion gradients whose concentration differs significantly from the rest of the body compartments [5]. To ensure these conditions, the CNS remains partially isolated by the existence of the blood-brain barrier (BBB), a highly complex semipermeable cellular barrier whose main function is to prevent both exogenous and endogenous elements to alter the brain homeostasis [5–7]. Regarding the immune response, microglial population constitutes the only immune system cellular representative within the brain with the astrocytes acting as a companion to exert immune surveillance and to act as the first line of response against harmful events within the brain. Although some additional peripheral immune cells including cluster of differentiation 11b and c (CD11b, CD11c)-positive cells localize to the CNS during some inflammatory conditions, it is believed that this situation is caused because of an altered permeability of the BBB as a consequence of the primary insult [8]. In this sense, the brain parenchyma has been defined as an anti-inflammatory environment due the increased levels of relevant anti-inflammatory mediators including the transforming growth factor β (TGF β) and interleukin (IL)-10, preventing both the immune cell spreading across the CNS and an excessively strong immune response [8–10]. However, this latter condition does not imply that the CNS cannot answer to immune challenges; on the contrary, the CNS is a fully immunocompetent system, but with this mechanism being tightly controlled in order to avoid secondary damage caused by extensive inflammation and detrimental cell damage end products, such as reactive oxygen

species (ROS). In this context, during the last years, it has been evidenced that sustained inflammatory challenge, whether systemic or local to the CNS, will alter significantly the neuronal environment affecting severely the neuronal function and the health of the neuronal network. Regrettably, it has been suggested that prior to AD and PD establishment as well as during their progression, a chronic inflammatory condition has developed, contributing to the molecular alterations observed during these pathologies.

3. Toll-like receptors

A significant characteristic of AD and PD is that these pathologies exhibit a strong inflammatory component even when both are sterile conditions. In this sense, the innate immune system works through the pattern recognition receptors (PRRs) which recognize molecular patterns related to pathogens (pathogen-associated molecular patterns, PAMPs) and to endogenous molecules indicative of cell damage (damage-associated molecular patterns, DAMPs), such as high-mobility group protein B1 (HMGB1), S100 proteins, heat shock proteins (HSPs), DNA, mitochondrial DNA (mt-DNA), and ATP [11–15]. The toll-like receptors (TLRs) family constitutes a highly relevant type of PRR necessary not only to unleash the initial immune response but also to connect the first unspecific defense with the secondary adaptive immunity [12].

Depending on the species, 11–13 TLR subtypes can be found. Relevantly, the localization of these receptors within the cells differs between the different TLRs. In this regard, while TLRs 1, 2, 4, 5, and 6 are expressed at the cell membrane, its main objective being to sense the extracellular compartment, the TLRs 3, 7, 8, and 9 are located inside the cells, mainly associated with endosomes and sensing the internal microenvironment for viral components, such as RNA and DNA [12, 16]. The presence of TLRs has been determined not only in several cell components of the peripheral immune system but also in the different cell types found in the brain including astrocytes, microglia, neurons, and oligodendrocytes, suggesting that each of these cell types can sense and trigger an immune response in the presence of different harmful molecular patterns. Interestingly, it has been demonstrated that not all the cells within the brain express the same pattern of TLRs. For example, microglia and neurons express all TLR subtypes, while astrocytes express a more limited repertoire, including TLR2, TLR3, TLR4, TLR9, and TLR11 [16, 17].

3.1 TLR inflammatory cascade

The signaling cascade triggered after TLRs' activation involves the cross talk with several additional pathways able to critically modify cell physiology. In this sense, canonical TLR-mediated signaling involves the myeloid differentiation factor 88 (MyD88) cascade. In this pathway, TLR activation couples with MyD88 inducing the activation of interleukin-1 receptor-associated kinase (IRAK) and, subsequently, the activation of the tumor necrosis factor receptor-associated factor 6. This event allows the recruitment of the transforming growth factor- β -activated kinase-1 (TAK1) which, together with the TAK1-binding proteins, leads to the phosphorylation of I κ B causing the activation of the IKK complex and the release of the nuclear factor- κ B (NF- κ B), triggering the NF- κ B-dependent inflammatory response [11, 18, 19]. Importantly, TLR 3 and TLR 4 can also signal via the TIR-containing adaptor inducing interferon- β (IFN- β) (TRIF). In this additional pathway, additional to the release of NF- κ B, it also causes an increased expression of IFN- β by means of the IKK ϵ /TANK-binding kinase-1 (TBK1)-dependent phosphorylation of the interferon regulatory factor 3 and 7 (IRF3 and IRF7) [7, 19, 20].

The main objective of these TLR-mediated processes is to regulate the expression of several pro-inflammatory and anti-inflammatory mediators including IL-1, IL-6, IL-10, IL-11, IL-12, tumor necrosis factor (TNF), TGF, IFN, CCL2, CCL5, CXCL8, and CXCL10, among others [4, 11, 18, 19].

Additionally, TLR activation can also signal through complementary molecular pathways. Indeed, TAK1 activation also induces nemo-like kinase (NLK) and the c-Jun N-terminal kinases (JNK) pathway [18–21]. Similarly, MyD88 can signal through the phosphatidylinositol-3 kinase (PI3K)/Akt pathway, modulating the activity of the glycogen synthase kinase 3 β (GSK3 β) [22, 23]. On the other hand, it has been demonstrated that TLR2 and TLR4 can activate the PI3K/Akt pathway through the Ras-related C3 botulinum toxin substrate 1 (Rac1), a member of the Rho family of GTPases [23]. Complementarily, the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) (JAK/STAT) pathway is known to respond to a variety of PAMPs/DAMPs and cytokines, including different interleukins and INF- β . Relevantly, different studies have demonstrated that several members of the TLR family can phosphorylate different STAT members, suggesting a direct modulation of the JAK/STAT pathway [24, 25]. As is possible to observe, the molecular cascades that could be triggered secondarily to TLR activation are related with critical cellular processes including cell cycle modulation, apoptosis, and cytoskeleton remodeling, among others. This situation depicts the complexity of the immune response and the relevance of its modulation in the context of different pathologies including neurodegenerative ones, such as AD and PD.

4. Alzheimer's and Parkinson's diseases: A β /SNCA and TLRs

4.1 Alzheimer's disease

AD constitutes the main form of dementia in the elderly population. Although, AD is recognized by the memory impairment and the reduced cognitive performance, the clinical scenario starts with mood alterations at the very beginning of the disease followed by the compromise of the short-term memory and the loss of long-term memory as the pathology progresses. Histologically, AD is characterized by the atrophy of the frontal cortex, limbic area, and hippocampus. On the other hand, the molecular hallmarks of AD are the formation of the amyloid- β (A β) plaques, constituted by the aggregated forms of the amyloid- β peptide, and the intraneuronal formation of neurofibrillary tangles (NFTs) composed of hyperphosphorylated tau protein [26]. Relevantly, beyond these hallmarks, AD also exhibits increased oxidative stress, mitochondrial dysfunction, and chronic inflammatory response. Altogether, these molecular alterations will lead to synaptic damage, neuronal loss, and neuronal circuitry breakdown [26, 27].

Relevantly, even when genetic conditions can lead to an early onset AD presentation, this accounts only for a small number of cases worldwide, with over 95% of the cases being termed as sporadic or late-onset AD. In this latter case, age and lifestyle have been defined as the main risk factors associated with the appearance of the disease [26, 27]. In agreement with the amyloid hypothesis of AD, these risk factors have a direct impact on the levels of A β leading to its increased production and subsequent accumulation within the brain [28, 29]. In this regard, different studies have linked the synaptic failure, mitochondrial dysfunction, tau hyperphosphorylation, glial activation, and neuronal death with increased levels of A β [27, 30]. Importantly, in the context of neuroinflammation, the ability of A β to induce the inflammatory response through the TLR2, TLR4, and TLR6, as well as their co-receptors including CD36, CD14, and CD47 has been widely demonstrated

[31–33]. However, it must be noticed that systemic inflammatory conditions have been linked with an increased risk of AD development, suggesting that the pro-inflammatory mediators are able to alter brain homeostasis leading to neuronal damage and to the beginning of the neurodegenerative process [34–38].

4.2 Parkinson's disease

PD corresponds to the second most common neurodegenerative disorder. PD is characterized by dopaminergic circuitry impairment caused by the loss of the dopaminergic neurons, mainly at the substantia nigra pars compacta (SNpc). Defined as synucleinopathy, PD exhibits neuronal inclusions of aggregated α -synuclein (SNCA) protein which can be located at the cell soma and/or neurites, forming the Lewy bodies and Lewy neurites [39]. SNCA plays relevant roles in the synaptic activity as it is linked with the recycling of synaptic vesicle pools [40–42]. Moreover, SNCA interferes with the dopamine metabolism affecting both the tyrosine hydroxylase, the enzyme in charge of synthesizing dopamine, and the dopamine transporter (DAT) [43, 44]. Similar to AD, even when the main signs of PD are associated with motor impairment, the pathological scenario begins much earlier with sleep disturbances and loss of olfaction which often passes unadvised to the patients or their relatives. Dementia is also an additional feature of the pathology and the affectation of memory can be part of the clinical picture. Although SNCA aggregation explains the damage to the dopaminergic neurons, the mechanisms behind SNCA dynamics have remained elusive [39, 45, 46]. Although PD can also emerge as a genetics-related disease with several genes linked to an early presentation, only a small proportion of the cases share this condition worldwide [39, 47]. In the same way, the vast majority of PD cases are linked to aging and lifestyle with the exposure of the patients to chemical xenobiotics, such as pesticides and recreational drugs being of most relevance [48]. Importantly, the SNCA aggregation is also related to the additional features observed during the pathological process, including mitochondrial dysfunction, increased oxidative stress, and neuroinflammation. Moreover, oxidative stress plays a central role in the pathophysiology of PD and the contribution of the ROS to the inflammatory milieu seems to be part of the establishment and progression of the disease.

Regarding the SNCA and inflammatory triggering, different researchers have demonstrated that depending on the aggregation status of SNCA, this protein can activate the TLRs, at least TLR2 and TLR4 [49–52]. Moreover, SNCA can be incorporated by the surrounding cells, particularly astrocytes, leading to the formation of SNCA inclusions also in these latter cells and helping to spread the SNCA pathology across the brain [53, 54]. Relevantly, PD can also be influenced by the systemic inflammatory status. Indeed, it has been recently demonstrated that increased levels of inflammatory mediators favor SNCA aggregation [55, 56].

4.3 A β /SNCA secondary inflammatory cascade

Although we have indicated that both A β and SNCA can activate the TLRs, we have only spoken about the direct activation induced by these molecules on some representatives of the TLR family. However, we must realize that once the TLRs are activated, a full repertory of pro-inflammatory mediators is released to the environment. In this context, A β induces the expression of IL-1, IL-6, IL-12, TNF- α , cyclooxygenase 2 (COX2), and the inducible nitric oxide synthase (iNOS) [57]. Additionally, because of the cellular damage caused, it will also induce the release of further DAMPs [26, 27, 58]. Similarly, TLRs activated after SNCA challenge will increase the expression of TNF- α , IL-6, and CXCL1 [49–51]. In the case of SNCA, the cell damage also will

cause the release of several DAMPs. Relevantly, the pro-inflammatory mediators and the subsequent DAMPs induced by A β and SNCA are able to further activate additional members of the TLR family, enhancing the inflammatory response. If we take into account that in both pathologies the levels of A β and SNCA are steadily increasing, the concept of a chronic inflammatory condition emerges as a potential mechanism to explain the progression of both diseases. Moreover, some of these pro-inflammatory mediators can also have a direct impact on the neuronal activity. Such is the case of the glial TNF- α -mediated expression of the AMPA receptors within the postsynaptic terminal. In this case, the increased production and release of TNF- α by the astrocytes, perhaps induced by the chronic exposure to the inflammatory stimulus, will cause the hyperexcitability of the neurons leading to glutamate excitotoxicity [59–62].

4.4 Microglial priming

Relevantly, an additional effect caused by A β and SNCA should be considered. It has been demonstrated that both molecules are also able to induce a phenomenon termed “microglial priming.” In this regard, microglial population which remains in a resting state when exposed to different inflammatory mediators, DAMPs, and/or PAMPs can differentiate into two activated phenotypes, the M1 and M2. While the M1 is considered as a pro-inflammatory activation state, the M2 is defined as the anti-inflammatory microglial phenotype. Interestingly, it has been evidenced that in the presence of INF- γ and the TLR-mediated signaling, microglia usually undergo M1 transformation. Moreover, when microglia became “primed” usually changes to the M2 phenotype but develops a significant sensibility to new exposures to harmful stimuli, exhibiting an over dimensioned response and causing the abnormal raising of pro-inflammatory molecules because of a shift to the M1 phenotype [63–66]. Thus, A β and SNCA seem to be favoring not only the activation of the microglia to the pro-inflammatory phenotype (M1), but also the increase in the responsiveness of the microglia to the harmful stimuli. In both cases, the result will be an over activation of the microglia with the subsequent release of increased levels of pro-inflammatory mediators and ROS, enhancing the damage induced by the initial exposure to A β and SNCA [67–69]. Similarly, the chronic exposure to these inflammatory mediators can induce the repolarization of the microglia changing from the M2 to the M1 phenotype [70]. However, additional research is necessary to properly address the significance of microglial priming and the effects of the exposure to different levels of pro-inflammatory stimuli [71]. Indeed, the work conducted by Pourbadie and cols. [72] seems to suggest that low doses of TLR ligands can exert beneficial effects on the neuronal circuitry.

4.5 Mitochondrial dysfunction

Another feature of both pathologies is the affectation of the mitochondrial functionality. Both A β and SNCA have the ability to interact with this critical organelle. While A β has been detected outside and inside the mitochondria being able to directly induce the several mitochondria-related apoptotic pathways, such as the B-cell lymphoma 2 (BCL2)-beclin1 (BECN1) complex [73, 74], SNCA can induce the activation of the mitochondrial membrane permeability transition pore, promoting mitochondrial swelling and leading to mitochondrial degradation. Indeed, when SNCA degradation is blocked by means of proteasome inhibition, mitochondria result as one of the first organelles to be affected. Moreover, TOM40, a protein that is part of the mitochondrial import machinery, has proven to be determinant of the SNCA-mediated mitochondrial failure [75–77]. Importantly, one of the most critical end points of the mitochondrial failure is the increased production of ROS

which is able to induce the activation of microglia and astrocytes as well as to trigger the inflammatory response mediated by the TLRs. Vice versa, the increased levels of pro-inflammatory mediators, such as TNF- α , induced by the activation of the TLRs by means of the A β and SNCA can also lead to mitochondrial dysfunction mainly through mitochondrial fragmentation [78].

5. Aging and neuroinflammation: self-conditioning to autodestruction?

Although aging constitutes a natural process, it has been considered from long ago as the main factor for several age-related conditions. However, we must realize that even when aging implies the progressive decay of several biological systems, the main issue with aging is the time span of exposure to different exogenous and potentially harmful stimuli (<http://www.iarc.fr>) [79, 80]. If we include the genetic and epigenetic heterogeneity between subjects as another factor to consider, it is almost evident that the aging process will follow different pathways depending on the particularities of each subject [81–83].

As previously mentioned, several works have evidenced the link between aging and neurodegenerative disorders. In the context of neuroinflammation, the immune system decay and a pro-inflammatory status are part of the aging process. Because of the increased levels of circulating inflammatory cytokines and the impaired performance of the cellular components involved in the immune response, a chronic exposure to an inflammatory environment verifies for all the biological systems. Regrettably, it has been demonstrated that the brain exhibits the same age-related pro-inflammatory deviation [84–87]. This general inflammatory status of the brain is currently termed as inflammaging.

In general terms, inflammaging is defined by the loss of the inflammatory homeostasis shifting to a pro-inflammatory condition with aging as the determinant factor. Moreover, it has been evidenced that inflammaging is caused by the deregulated function of the inflammasomes, the intracellular structures where several pro-inflammatory mediators are synthesized including several cytokines [84, 88–90]. Moreover, some works have also suggested that inflammaging involves not the deregulation of TLR expression, but the signal cascades triggered after its activation through different microRNAs [91].

On the other hand, inflammaging can also relate with cell senescence. Regrettably, cell senescence also verifies in the immune system and affects the immune cells of both the peripheral system and the CNS. Although astrocytes are believed to be the only cells able to express senescence markers, different researches have evidenced that microglia also exhibit several age-related morphological and biochemical changes. Indeed, the increased levels of activation markers including the cluster of differentiation 11b, 11c, and 14, along with the increased production of TNF- α , IL-1 β , IL-6, and reactive oxygen species (ROS) allow to dimension the effect of senescence on the physiology of the immunocompetent cells within the brain [92].

6. Concluding remarks

Inflammatory milieu is an extremely complex event. Moreover, it becomes even more complicated when we introduce the neurodegenerative process as part of the inflammatory equation. In this case, the final outcome will not only be determined by the production and release of the pro-inflammatory mediators and the specific responses triggered in the different cell types present in the brain, but it will also depend on the physiological status of these cells. Aging, and the differential exposure

to xenobiotics, will certainly determine the health status of the cells and its ability to answer properly to the inflammatory stimulus and to resist a pro-inflammatory condition. At the basis of all these processes, the molecular mechanisms triggered by the TLRs play a critical role during both AD and PD establishment and progression. Moreover, through the cross talk with additional signaling pathways, TLR cascade is able to interfere with different aspects of the cell physiology from energy production to cytoskeleton rearrangements. On the other hand, less is known regarding other representatives of the TLR family and their impact on AD/PD pathophysiology. For example, some evidence seems to suggest that while TLR9 will exert a protective effect in the context of the neurodegenerative process driven by A β and SNCA, TLR3 will also enhance the release of pro-inflammatory mediators [93].

To date, significant evidence seems to confirm the key role of the inflammatory milieu in the neurodegenerative process and this situation should prompt researchers to increase their efforts to understand this cascade of events and to unveil the missing points of an inflammatory-based hypothesis of the neurodegenerative disorders.

Conflicts of interest

The authors declare no competing interest regarding the publication of this work.

Funding

This work was supported by grants from the Basal Center of Excellence in Aging and Regeneration AFB 170005 and FONDECYT (no. 1160724) to NCI and by FONDECYT N° 11170212 to SBC.

Author details

Juan M. Zolezzi¹, Sussy Bastías-Candia¹ and Nibaldo C. Inestrosa^{1,2,3*}

¹ Faculty of Biological Sciences, Department of Cellular and Molecular Biology, Center for Aging and Regeneration (CARE Chile UC), P. Catholic University of Chile, Santiago, Chile

² Faculty of Medicine, School of Psychiatry, Centre for Healthy Brain Ageing, University of New South Wales, Sydney, Australia

³ Center for Excellence in Biomedicine of Magellan (CEBIMA), University of Magallanes, Punta Arenas, Chile

*Address all correspondence to: ninestrosa@bio.puc.cl

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

References

- [1] Alzheimer's Disease International. World Alzheimer Report. 2016. Available from: <https://www.alz.co.uk/research/world-report> [Accessed: December 20, 2018]
- [2] Heneka MT, Golenbock DT, Latz E. Innate immunity in Alzheimer's disease. *Nature Immunology*. 2015;**16**:229-236. DOI: 10.1038/ni.3102
- [3] Heneka MT, Carson MJ, El Khoury J, Landreth GE, Brosseron F, Feinstein DL, et al. Neuroinflammation in Alzheimer's disease. *Lancet Neurology*. 2015;**14**:388-405. DOI: 10.1016/S1474-4422(15)70016-5
- [4] Ardura-Fabregat A, Boddeke EWGM, Boza-Serrano A, Brioschi S, Castro-Gomez S, Ceyzeriat K, et al. Targeting neuroinflammation to treat Alzheimer's disease. *CNS Drugs*. 2017;**12**:1057-1082. DOI: 10.1007/s40263-017-0483-3
- [5] Abbott NJ, Patabendige AA, Dolman DE, Yusof SR, Begley DJ. Structure and function of the blood-brain barrier. *Neurobiology of Disease*. 2010;**37**:13-25. DOI: 10.1016/j.nbd.2009.07.030
- [6] Zolezzi JM, Inestrosa NC. Peroxisome proliferator-activated receptors and Alzheimer's disease: Hitting the blood-brain barrier. *Molecular Neurobiology*. 2013;**48**:438-451. DOI: 10.1007/s12035-013-8435-5
- [7] Nation DA, Sweeney MD, Montagne A, Sagare AP, D'Orazio LM, Pachicano M, et al. Blood-brain barrier breakdown is an early biomarker of human cognitive dysfunction. *Nature Medicine*. 2019;**25**:270-276. DOI: 10.1038/s41591-018-0297-y
- [8] Ransohoff R, Brown M. Innate immunity in the central nervous system. *Journal of Clinical Investigation*. 2012;**122**:1164-1171. DOI: 10.1172/JCI58644
- [9] Strle K, Zhou JH, Shen WH, Broussard SR, Johnson RW, Freund GG, et al. Interleukin-10 in the brain. *Critical Reviews in Immunology*. 2001;**21**:427-449. DOI: 10.1615/CritRevImmunol.v21.i5.20
- [10] Malipiero U, Koedel U, Pfister HW, Levéen P, Bürki K, Reith W, et al. TGFbeta receptor II gene deletion in leucocytes prevents cerebral vasculitis in bacterial meningitis. *Brain*. 2006;**129**:2404-2415. DOI: 10.1093/brain/awl192
- [11] Landreth G, Reed-Geaghan E. Toll-like receptors in Alzheimer's disease. *Current Topics in Microbiology and Immunology*. 2009;**336**:137-153. DOI: 10.1007/978-3-642-00549-7_8
- [12] Hanke M, Kielian T. Toll-like receptors in health and disease in the brain: Mechanisms and therapeutic potential. *Clinical Science (London)*. 2011;**121**:367-387. DOI: 10.1042/CS20110164
- [13] Takeuchi O, Akira S. Pattern recognition receptors and inflammation. *Cell*. 2010;**140**:805-820. DOI: 10.1016/j.cell.2010.01.022
- [14] Piccinini AM, Midwood KS. DAMPening inflammation by modulating TLR signaling. *Mediators of Inflammation*. 2010;**2010**:pii:672395. DOI: 10.1155/2010/672395
- [15] Bianchi ME. DAMPs, PAMPs and alarmins: All we need to know about danger. *Journal of Leukocyte Biology*. 2007;**81**:1-5. DOI: 10.1189/jlb.0306164
- [16] Atmaca HT, Kul O, Karakus E, Terzi OS, Canpolat S, Anteplioglu T. Astrocytes, microglia/macrophages, and neurons expressing toll-like receptor

- 11 contribute to innate immunity against encephalitic toxoplasma gondii infection. *Neuroscience*. 2014;**269**:184-191. DOI: 10.1016/j.neuroscience.2014.03.049
- [17] Mishra BB, Mishra PK, Teale JM. Expression and distribution of toll-like receptors in the brain during murine neurocysticercosis. *Journal of Neuroimmunology*. 2006;**181**:46-56. DOI: 10.1016/j.jneuroim.2006.07.019
- [18] Kawai T, Akira S. Toll-like receptor downstream signaling. *Arthritis Research and Therapy*. 2005;**7**:12-19. DOI: 10.1186/ar1469
- [19] Kawai T, Akira S. Signaling to NF- κ B by toll-like receptors. *Trends in Molecular Medicine*. 2007;**13**:460-469. DOI: 10.1016/j.molmed.2007.09.002
- [20] Ishitani T, Ninomiya-Tsuji J, Nagai S, Nishita M, Meneghini M, Barker N, et al. The TAK1-NLK-MAPK-related pathway antagonizes signaling between β -catenin and transcription factor TCF. *Nature*. 1999;**399**:798-802. DOI: 10.1038/21674
- [21] Zhang ZY, Li SZ, Zhang HH, Wu QR, Gong J, Liang T, et al. Stabilization of ATF5 by TAK1-Nemo-like kinase critically regulates the interleukin-1 β -stimulated C/EBP signaling pathway. *Molecular and Cellular Biology*. 2015;**35**:778-788. DOI: 10.1128/MCB.01228-14
- [22] Monick MM, Carter AB, Robeff PK, Flaherty DM, Peterson MW, Hunninghake GW. Lipopolysaccharide activates Akt in human alveolar macrophages resulting in nuclear accumulation and transcriptional activity of beta-catenin. *Journal of Immunology*. 2001;**166**:4713-4720. DOI: 10.4049/jimmunol.166.7.4713
- [23] Arbibe L, Mira JP, Teusch N, Kline L, Guha M, Mackman N, et al. Toll-like receptor 2-mediated NF-kappa B activation requires a Rac1-dependent pathway. *Nature Immunology*. 2000;**1**:533-540. DOI: 10.1038/82797
- [24] Luu K, Greenhill CJ, Majorors A, Decker T, Jenkins BJ, Mansell A. STAT1 plays a role in TLR signal transduction and inflammatory responses. *Immunology and Cell Biology*. 2014;**92**:761-769. DOI: 10.1038/icb.2014.51
- [25] Song F, Zeng K, Liao L, Yu Q, Tu P, Wang X. Schizadrin a inhibits microglia-mediated neuroinflammation through inhibiting TRAF6-NF- κ B and Jak-Stat3 signaling pathways. *PLoS One*. 2016;**11**:1-16. DOI: 10.1371/journal.pone.0149991
- [26] Selkoe DJ. Alzheimer's disease. *Cold Spring Harbor Perspectives in Biology*. 2011;**3**:a004457. DOI: 10.1101/cshperspect.a004457
- [27] Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Molecular Medicine*. 2016;**8**:595-608. DOI: 10.15252/emmm.201606210
- [28] Singh I, Sagare AP, Coma M, Perlmutter D, Gelein R, Bell RD, et al. Low levels of copper disrupt brain amyloid- β homeostasis by altering its production and clearance. *Proceedings of the National Academy of Sciences of the United States of America*. 2013;**110**:14771-14776. DOI: 10.1073/pnas.1302212110
- [29] Yan R, Vassar R. Targeting the β secretase BACE1 for Alzheimer's disease therapy. *Lancet Neurology*. 2014;**13**:319-329. DOI: 10.1016/S1474-4422(13)70276-X
- [30] Zolezzi JM, Bastías-Candia S, Santos MJ, Inestrosa NC. Alzheimer's disease: Relevant molecular and physiopathological events affecting amyloid- β brain balance and the putative role of PPARs. *Frontiers in Aging Neuroscience*. 2014;**6**:176. DOI: 10.3389/fnagi.2014.00176

- [31] Salminen A, Ojala J, Kauppinen A, Kaarniranta K, Suuronen T. Inflammation in Alzheimer's disease: Amyloid-beta oligomers trigger innate immunity defense via pattern recognition receptors. *Progress in Neurobiology*. 2009;**87**:181-194. DOI: 10.1016/j.pneurobio.2009.01.001
- [32] Liu S, Liu Y, Hao W, Wolf L, Kiliaan AJ, Penke B, et al. TLR2 is a primary receptor for Alzheimer's amyloid b peptide to trigger neuroinflammatory activation. *Journal of Immunology*. 2012;**188**:1098-1107. DOI: 10.4049/jimmunol.1101121
- [33] Fassbender K, Walter S, Kühl S, Landmann R, Ishii K, Bertsch T, et al. The LPS receptor (CD14) links innate immunity with Alzheimer's disease. *FASEB Journal*. 2004;**18**:203-205. DOI: 10.1096/fj.03-0364fje
- [34] Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *Journal of the American Medical Association*. 2010;**304**:1787-1794. DOI: 10.1001/jama.2010.1553
- [35] McManus RM, Heneka MT. Role of neuroinflammation in neurodegeneration: New insights. *Alzheimer's Research & Therapy*. 2017;**9**:14. DOI: 10.1186/s13195-017-0241-2
- [36] Dunn N, Mullee M, Perry VH, Holmes C. Association between dementia and infectious disease: Evidence from a case-control study. *Alzheimer Disease and Associated Disorders*. 2005;**19**:91-94. DOI: 10.1097/01.wad.0000165511.52746.1f
- [37] Holmes C, El-Okli M, Williams AL, Cunningham C, Wilcockson D, Perry VH. Systemic infection, interleukin 1beta, and cognitive decline in Alzheimer's disease. *Journal of Neurology, Neurosurgery and Psychiatry*. 2003;**74**:788-789. DOI: 10.1136/jnnp.74.6.788
- [38] Holmes C, Cunningham C, Zotova E, Woolford J, Dean C, Kerr S, et al. Systemic inflammation and disease progression in Alzheimer disease. *Neurology*. 2009;**73**:768-774. DOI: 10.1212/WNL.0b013e3181b6bb95
- [39] Kalia LV, Lang AE. Parkinson's disease. *Lancet*. 2015;**386**:896-912. DOI: 10.1016/S0140-6736(14)61393-3
- [40] Murphy DD, Rueter SM, Trojanowski JQ, Lee VM. Synucleins are developmentally expressed, and alpha-synuclein regulates the size of the presynaptic vesicular pool in primary hippocampal neurons. *The Journal of Neuroscience*. 2000;**20**:3214-3220. DOI: 10.1523/JNEUROSCI.20-09-03214.2000
- [41] Cabin DE, Shimazu K, Murphy D, Cole NB, Gottschalk W, McIlwain KL, et al. Synaptic vesicle depletion correlates with attenuated synaptic responses to prolonged repetitive stimulation in mice lacking alpha-synuclein. *The Journal of Neuroscience*. 2002;**22**:8797-8807. DOI: 10.1523/JNEUROSCI.22-20-08797.2002
- [42] Larsen KE, Schmitz Y, Troyer MD, Mosharov E, Dietrich P, Quazi AZ, et al. Alpha-synuclein overexpression in PC12 and chromaffin cells impairs catecholamine release by interfering with a late step in exocytosis. *The Journal of Neuroscience*. 2006;**26**:11915-11922. DOI: 10.1523/JNEUROSCI.3821-06.2006
- [43] Li YH, Gao N, Ye YW, Li X, Yu S, Yang H, et al. Alpha-synuclein functions as a negative regulator for expression of tyrosine hydroxylase. *Acta Neurologica Belgica*. 2011;**111**:130-135
- [44] Butler B, Goodwin S, Saha K, Becker J, Sambo D, Davari P, et al. Dopamine transporter activity is modulated by alpha-synuclein.

The Journal of Biological Chemistry. 2015;**290**:29542-29554. DOI: 10.1074/jbc.M115.691592

[45] Jia SH, Li K, Su W, Li SH, Chen HB. Impairment in the intention formation and execution phases of prospective memory in Parkinson's disease. *Frontiers in Neuroscience*. 2018;**12**:98. DOI: 10.3389/fnins.2018.00098

[46] Hawkes CH, Del Tredici K, Braak H. A timeline for Parkinson's disease. *Parkinsonism & Related Disorders*. 2010;**16**:79-84. DOI: 10.1016/j.parkreldis.2009.08.007

[47] Bridi JC, Hirth F. Mechanisms of α -synuclein induced synaptopathy in Parkinson's disease. *Frontiers in Neuroscience*. 2018;**12**:80. DOI: 10.3389/fnins.2018.00080

[48] Bastías-Candia S, Di Benedetto M, D'Addario C, Candeletti S, Romualdi P. Combined exposure to agriculture pesticides, paraquat and maneb, induces alterations in the N/OFQ-NOPr and PDYN/KOPr systems in rats: Relevance to sporadic Parkinson's disease. *Environmental Toxicology*. 2015;**30**: 656-663. DOI: 10.1002/tox.21943

[49] Stefanova N, Fellner L, Reindl M, Masliah E, Poewe W, Wenning GK. Toll-like receptor 4 promotes α -synuclein clearance and survival of nigral dopaminergic neurons. *The American Journal of Pathology*. 2011;**179**:954-963. DOI: 10.1016/j.ajpath.2011.04.013

[50] Fellner L, Irschick R, Schanda K, Reindl M, Klimaschewski L, Poewe W, et al. Toll-like receptor 4 is required for α -synuclein dependent activation of microglia and astroglia. *Glia*. 2013;**61**:349-360. DOI: 10.1002/glia.22437

[51] Kim C, Ho DH, Suk JE, You S, Michael S, Kang J, et al. Neuron-released oligomeric α -synuclein is

an endogenous agonist of TLR2 for paracrine activation of microglia. *Nature Communications*. 2013;**4**:1562. DOI: 10.1038/ncomms2534

[52] Sanchez-Guajardo V, Tentillier N, Romero-Ramos M. The relation between α -synuclein and microglia in Parkinson's disease: Recent developments. *Neuroscience*. 2015;**302**:47-58. DOI: 10.1016/j.neuroscience.2015.02.008

[53] Ganguly U, Chakrabarti SS, Kaur U, Mukherjee A, Chakrabarti S. Alpha-synuclein, proteotoxicity and Parkinson's disease: Search for neuroprotective therapy. *Current Neuropharmacology*. 2017;**15**. DOI: 10.2174/1570159X15666171129100944

[54] Lee HJ, Suk JE, Patrick C, Bae EJ, Cho JH, Rho S, et al. Direct transfer of alpha-synuclein from neuron to astroglia causes inflammatory responses in synucleinopathies. *The Journal of Biological Chemistry*. 2010;**285**: 9262-9272. DOI: 10.1074/jbc.M109.081125

[55] Bassil F, Fernagut PO, Bezard E, Pruvost A, Leste-Lasserre T, Hoang QQ, et al. Reducing C-terminal truncation mitigates synucleinopathy and neurodegeneration in a transgenic model of multiple system atrophy. *Proceedings of the National Academy of Sciences of the United States of America*. 2016;**113**:9593-9598. DOI: 10.1073/pnas.1609291113

[56] Wang W, Nguyen LT, Burlak C, Chegini F, Guo F, Chataway T, et al. Caspase-1 causes truncation and aggregation of the Parkinson's disease-associated protein α -synuclein. *Proceedings of the National Academy of Sciences of the United States of America*. 2016;**113**:9587-9592. DOI: 10.1073/pnas.1610099113

[57] Reed-Geaghan EG, Savage JC, Hise AG, Landreth GE. CD14 and

toll-like receptors 2 and 4 are required for fibrillar Ab-stimulated microglial activation. *Journal of Neuroscience*. 2009;**29**:11982-11992. DOI: 10.1523/JNEUROSCI.3158-09.2009

[58] Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nature Reviews Neurology*. 2018;**14**:133-150. DOI: 10.1038/nrneurol.2017.188

[59] Yirmiya R, Goshen I. Immune modulation of learning, memory, neural plasticity and neurogenesis. *Brain, Behavior, and Immunity*. 2011;**25**: 181-213. DOI: 10.1016/j.bbi.2010.10.015

[60] Turrigiano GG. The self-tuning neuron: Synaptic scaling of excitatory synapses. *Cell*. 2008;**135**:422-435. DOI: 10.1016/j.cell.2008.10.008

[61] Stellwagen D, Malenka RC. Synaptic scaling mediated by glial TNF- α . *Nature*. 2006;**440**:1054-1059. DOI: 10.1038/nature04671

[62] Riazi K, Galic MA, Kuzmiski JB, Ho W, Sharkey KA, Pittman QJ. Microglial activation and TNF α production mediate altered CNS excitability following peripheral inflammation. *Proceedings of the National Academy of Sciences of the United States of America*. 2008;**105**: 17151-17156. DOI: 10.1073/pnas.0806682105

[63] Ajami B, Bennett JL, Krieger C, et al. Local self-renewal can sustain CNS microglia maintenance and function throughout adult life. *Nature Neuroscience*. 2007;**10**:1538-1543. DOI: 10.1038/nn2014

[64] Lynch MA. The multifaceted profile of activated microglia. *Molecular Neurobiology*. 2009;**40**:139-156. DOI: 10.1007/s12035-009-8077-9

[65] Perry VH. Contribution of systemic inflammation to

chronic neurodegeneration. *Acta Neuropathologica*. 2010;**120**:277-286. DOI: 10.1007/s00401-010-0722-x

[66] Ghosh S, Wu MD, Shafteel SS, et al. Sustained interleukin-1 β overexpression exacerbates tau pathology despite reduced amyloid burden in an Alzheimer's mouse model. *Journal of Neuroscience*. 2013;**33**:5053-5064. DOI: 10.1523/JNEUROSCI.4361-12.2013

[67] Rojanathammanee L, Floden AM, Manocha GD, et al. Attenuation of microglial activation in a mouse model of Alzheimer's disease via NFAT inhibition. *Journal of Neuroinflammation*. 2015;**12**:42. DOI: 10.1186/s12974-015-0255-2

[68] Wu Z, Sun L, Hashioka S, et al. Differential pathways for interleukin-1 β production activated by chromogranin a and amyloid β in microglia. *Neurobiology of Aging*. 2013;**34**:2715-2725. DOI: 10.1016/j.neurobiolaging.2013.05.018

[69] Rocha EM, Smith GA, Park E, et al. Sustained systemic glucocerebrosidase inhibition induces brain α -synuclein aggregation, microglia and complement C1q activation in mice. *Antioxidants and Redox Signaling*. 2015;**23**:550-564. DOI: 10.1089/ars.2015.6307

[70] Perry VH, Teeling J. Microglia and macrophages of the central nervous system: The contribution of microglia priming and systemic inflammation to chronic neurodegeneration. *Seminars in Immunopathology*. 2013;**35**:601-612. DOI: 10.1007/s00281-013-0382-8

[71] Caldeira C, Cunha C, Vaz AR, Falcão AS, Barateiro A, Seixas E, et al. Key aging-associated alterations in primary microglia response to β -amyloid stimulation. *Frontiers in Aging Neuroscience*. 2017;**9**:277. DOI: 10.3389/fnagi.2017.00277

- [72] Pourbadie HG, Sayyah M, Khoshkholgh-Sima B, Choopani S, Nategh M, Motamedi F, et al. Early minor stimulation of microglial TLR2 and TLR4 receptors attenuates Alzheimer's disease-related cognitive deficit in rats: Behavioral, molecular, and electrophysiological evidence. *Neurobiology of Aging*. 2018;**70**:203-216. DOI: 10.1016/j.neurobiolaging.2018.06.020
- [73] Cai Q, Tammineni P. Mitochondrial aspects of synaptic dysfunction in Alzheimer's disease. *Journal of Alzheimer's Disease*. 2017;**57**:1087-1103. DOI: 10.3233/JAD-160726
- [74] Kerr JS, Adriaanse BA, Greig NH, Mattson MP, Cader MZ, Bohr VA, et al. Mitophagy and Alzheimer's disease: Cellular and molecular mechanisms. *Trends in Neurosciences*. 2017;**40**:151-166. DOI: 10.1016/j.tins.2017.01.002
- [75] Banerjee K, Sinha M, Pham CLL, Jana S, Chanda D, Cappai R, et al. Alpha-synuclein induced membrane depolarization and loss of phosphorylation capacity of isolated rat brain mitochondria: Implications in Parkinson's disease. *FEBS Letters*. 2010;**584**:1571-1576. DOI: 10.1111/jnc.12966
- [76] Bender A, Desplats P, Spencer B, et al. TOM40 mediates mitochondrial dysfunction induced by α -synuclein accumulation in Parkinson's disease. *PLoS One*. 2013;**8**:e62277. DOI: 10.1371/journal.pone.0062277
- [77] Junn E, Mouradian MM. Human α -Synuclein over-expression increases intracellular reactive oxygen species levels and susceptibility to dopamine. *Neuroscience Letters*. 2002;**320**:146-150. DOI: 10.1016/S0304-3940(02)00016-2
- [78] Wu B, Li J, Ni H, Zhuang X, Qi Z, Chen Q, et al. TLR4 activation promotes the progression of experimental autoimmune myocarditis to dilated cardiomyopathy by inducing mitochondrial dynamic imbalance. *Oxidative Medicine and Cellular Longevity*. 2018;**2018**:3181278. DOI: 10.1155/2018/3181278
- [79] Liu Y-Z, Wang Y-X, Jiang C-L. Inflammation: The common pathway of stress-related diseases. *Frontiers in Human Neuroscience*. 2017;**11**:316. DOI: 10.3389/fnhum.2017.00316
- [80] McCormick CM, Hodges TE. Stress, glucocorticoids, and brain development in rodent models. In: Fink G, editor. *Stress: Neuroendocrinology and Neurobiology*. San Diego: Academic Press; 2017. pp. 197-206
- [81] Ashapkin VV, Kutueva LI, Vanyushin BF. Aging as an epigenetic phenomenon. *Current Genomics*. 2017;**18**:385-407. DOI: 10.2174/1389202918666170412112130
- [82] Masser DR, Hadad N, Porter HL, Mangold CA, Unnikrishnan A, Ford MM, et al. Sexually divergent DNA methylation patterns with hippocampal aging. *Aging Cell*. 2017;**16**:1342-1352. DOI: 10.1111/accel.12681
- [83] Lunnon K, Smith R, Hannon E, De Jager PL, Srivastava G, Volta M, et al. Methyloomic profiling implicates cortical deregulation of ANK1 in Alzheimer's disease. *Nature Neuroscience*. 2014;**17**:1164-1170. DOI: 10.1038/nn.3782
- [84] Cao W, Zheng H. Peripheral immune system in aging and Alzheimer's disease. *Molecular Neurodegeneration*. 2018;**1**:51. DOI: 10.1186/s13024-018-0284-2
- [85] Schwalm MT, Pasquali M, Miguel SP, Dos Santos JP, Vuolo F, Comim CM, et al. Acute brain inflammation and oxidative damage are related to long-term cognitive deficits and markers of neurodegeneration in sepsis-survivor rats. *Molecular Neurobiology*.

2014;**49**:380-385. DOI: 10.1007/s12035-013-8526-3

[86] Wang LM, Wu Q, Kirk RA, Horn KP, Ebada Salem AH, Hoffman JM, et al. Lipopolysaccharide endotoxemia induces amyloid- β and p-tau formation in the rat brain. *American Journal of Nuclear Medicine and Molecular Imaging*. 2018;**8**:86-99. ISSN:2160-8407/ajnm0074312

[87] Wyss-Coray T. Ageing, neurodegeneration and brain rejuvenation. *Nature*. 2016;**539**:180-186. DOI: 10.1038/nature20411

[88] Giunta B, Fernandez F, Nikolic WV, Obregon D, Rapo E, Town T, et al. Inflammaging as a prodrome to Alzheimer's disease. *Journal of Neuroinflammation*. 2008;**5**:51. DOI: 10.1186/1742-2094-5-51

[89] Frasca D, Blomberg BB. Inflammaging decreases adaptive and innate immune responses in mice and humans. *Biogerontology*. 2016;**17**: 7-19. DOI: 10.1007/s10522-015-9578-8

[90] Yao H, Rahman I. Perspectives on translational and therapeutic aspects of SIRT1 in inflammaging and senescence. *Biochemical Pharmacology*. 2012;**84**:1332-1339. DOI: 10.1016/j.bcp.2012.06.031

[91] Olivieri F, Rippo MR, Prattichizzo F, Babini L, Graciotti L, Recchioni R, et al. Toll like receptor signaling in "inflammaging": microRNA as new players. *Immunity & Ageing*. 2013;**10**:11. DOI: 10.1186/1742-4933-10-11

[92] Cameron B, Landreth GE. Inflammation, microglia, and Alzheimer's disease. *Neurobiology of Disease*. 2010;**37**:503-509. DOI: 10.1016/j.nbd.2009.10.006

[93] Walker DG, Tang TM, Lue LF. Increased expression of toll-like receptor

3, an anti-viral signaling molecule, and related genes in Alzheimer's disease brains. *Experimental Neurology*. 2018;**309**:91-106. DOI: 10.1016/j.expneurol.2018.07.016