Chapter

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

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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-1α), 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 (TGFβ) 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 IκB causing the activation of the IKK complex and the release of the nuclear factor-κB (NF-κB), triggering the NF-κB-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-κB, it also causes an increased expression of IFN-β by means of the IKKε/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 phosphatidylinositide-3 kinase (PI3K)/Akt pathway, modulating the activity of the glycogen synthase kinase 3 β (GSK3β) [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]. Complimentarily, 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: Aβ/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 (Aβ) 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 Aβ 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 Aβ [27, 30]. Importantly, in the context of neuroinflammation, the ability of Aβ 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 to 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 synthetizing 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 Aβ/SNCA secondary inflammatory cascade

Although we have indicated that both Aβ 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, Aβ 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 Aβ 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 Aβ 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 Aβ 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, Aβ 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 Aβ 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 Aβ and SNCA have the ability to interact with this critical organelle. While Aβ 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 Aβ 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 synthetized 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-1β, 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 Aβ 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.

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