Targeting Microglia-Synapse Interactions

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Synaptic plasticity refers to the capability of experience to modify neural circuit function and thereby influence thinking, feeling, and behavioral patterns.

microglia Alzheimer's disease synaptic plasticity

1. Introduction

Long-term potentiation (LTP) and long-term depression (LTD) of synaptic transmission represent the principal experimental model for the synaptic changes underlying learning and memory [1][2]. It is widely recognized that alterations in normal synaptic function are not only a core feature, but also a leading cause of several neuropsychiatric diseases, including Alzheimer's disease (AD) [3].

Microglia, a specialized population of cells present in the central nervous system, are considered immune sentinels which mediate a potent inflammatory response, but are also involved in many central processes as synaptic organization, trophic neuronal support during development, and the control of neuronal excitability [4].

Neuroinflammatory stimuli that occur in neurodegenerative process can alter synaptic plasticity through alteration of microglia immune-related pathways [5]. Indeed, the close interactions between microglia and synapses lead to the so-called synaptic stripping hypothesis [6], a process in which microglia can selectively eliminate dysfunctional synapses. This microglia-mediated synapse removal, normally associated with activity-dependent refinement during neurodevelopment, can be reactivated in aging or in neurodegenerative diseases [7].

2. Microglia and Neuroinflammation in AD

2.1. Microglia in Brain Physiology

Different populations of macrophages deal with heterogeneous functions in the maintenance of the brain homeostasis. Among them, microglia cells are the principal type located in the central nervous system (CNS) parenchyma, where they are connected with neurons, astrocytes and oligodendrocytes [8].

During brain development, microglial cells originate from blood-derived precursors and require colony-stimulating factor 1 receptor (CSF1R) signaling for their proliferation and survival [9]. These progenitors invade the neural tissue and are distributed throughout the CNS acquiring a ramified phenotype known as resting microglia [10].

Microglia are involved in several processes in both healthy and pathological brain. Specifically, it plays a crucial role in the maintenance of appropriate synaptic connections and neuronal plasticity. Indeed, through the development of the visual system, microglia prune out the presynaptic inputs that originate from the retinal ganglion cells (RGCs) into the dorsal lateral geniculate nucleus (LGN), such that each LGN neuron receive inputs from one RGCs [11]. This mechanism of elimination/pruning of unused and immature connections is thought to be responsible for the correct efficiency of neuronal transmission during brain development [9]. Synaptic turnover mediated by microglia has been also observed during adulthood, a mechanism by which microglia seems to be involved in maintenance of the physiological neuronal activity and synaptic plasticity by influencing the LTP and LTD process [12][13], even though the underlying mechanisms remain elusive.

During the developmental synaptic pruning process, microglia directly contact synapses via specific molecular pathways. The main one involves the classical complement cascade: C1q and C3 complement proteins localize to the afferent terminals that need to be removed, representing an “eat me” signal for microglia, which express the C3 receptor (C3R) [14].

In addition to synaptic refinement, microglial cells are specialized in maintaining cerebral homeostasis through the induction of immune responses. Under normal conditions, immune responses evoked by microglia and macrophages act in a coordinated manner to elicit the first line of defense against toxic insults from both internal and external sources [15]. Indeed, in response to pathologic stimuli, loss of homeostasis or tissue changes, microglia change their morphology, antigen presentation, and phagocytic and secretory activity [16]. In such conditions, microglia activation is driven by pro- or anti-inflammatory molecules that behave as damage- and pathogen-associated molecular patterns (DAMPs-PAMPs) [17]. These molecules bind to pattern recognition receptors (PRRs) expressed by microglia, thus signaling the presence of a CNS insult and initiating an immune response [18].

In the brain, microglia cells can exist in two different states, “resting” and “activated” microglia. The first is characterized by branched morphology and is present in healthy brains while the latter has an amoeboid morphology and is typical of unhealthy brains [19]. Resting microglia have a low expression of surface receptors, such as the complement receptor CD45, CD14, and Mac-1 (CD11b/CD18) [20]. Microglia cells sense microenvironmental changes and respond to pathogens and injuries by becoming ‘‘activated’’, a process through which they rapidly change their ramified morphology to an amoeboid phenotype and migrate to the lesioned site, where they phagocytize pathogens [21]. Traditionally, two distinct and opposite phenotypes, neurotoxic (M1) and neuroprotective (M2), are identifiable for “activated microglia” which differ in terms of receptor expression, effector function as well as cytokine and chemokine production [22]. Depending on the received stimuli, microglia can be classically or alternatively activated, thereby having opposite roles in the CNS. Several experiments investigated the different polarization of microglia, showing how the stimulation with lipopolysaccharide (LPS) or interferon (IFN) γ induces the activation of the neurotoxic M1 phenotype, whereas IL-4 or IL-13 induces the neuroprotective M2 activation [23].

The M1 polarization, often called “classical activation”, is a pro-inflammatory state induced mainly in response to injuries and infections and acts as the first line of tissue defense [24]. This activation causes inflammation and consequent cytotoxicity by release of reactive oxygen species (ROS), nitrogen reactive species (NRS), nitric oxide (NO), pro-inflammatory cytokines, and chemokines including TNF-α, IL-1β, IL-6, IL-12, and IL-18. Additionally, it is accompanied by impaired phagocytic capacity [25] and decrease of neurotrophic factors release.

In contrast, an anti-inflammatory phase is promptly initiated to antagonize the pro-inflammatory responses and restore tissue homeostasis [24]. Indeed, the M2 polarization, referred as “alternative activation”, is characterized by secretion of cytokines with anti-inflammatory activity such as IL-4, IL-10, IL-13, transforming growth factor (TGF) β, growth factors (insulin-like growth factor, IGF-1; fibroblast growth factor, FGF; Colony-stimulating factor, CSF1), and neurotrophic growth factor (brain-derived neurotrophic factor, BDNF; glial cell-derived neurotrophic factor, GDNF). Of interest, IL-4 and IL-13 present anti-inflammatory proprieties which could suppress the production of some of the pro-inflammatory cytokines produced by M1 phenotype [26] and reduce NO release, protecting against neuron injury induced by LPS [27]. In turn, IL-4 and IL-13 stimulate microglia- M2 phenotype [28] and cause the expression of arginase (Arg) 1, Ym-1, CD200R, IL-10, TGFβ, and Fizzl-1, which serve as specific markers for M2 microglia. In this way, microglia can be neuroprotective and neurosupportive via different mechanisms that include glutamate uptake, removal of dead cells and accumulation of abnormal proteins or production of neurotrophic factors [19] (Figure 1).

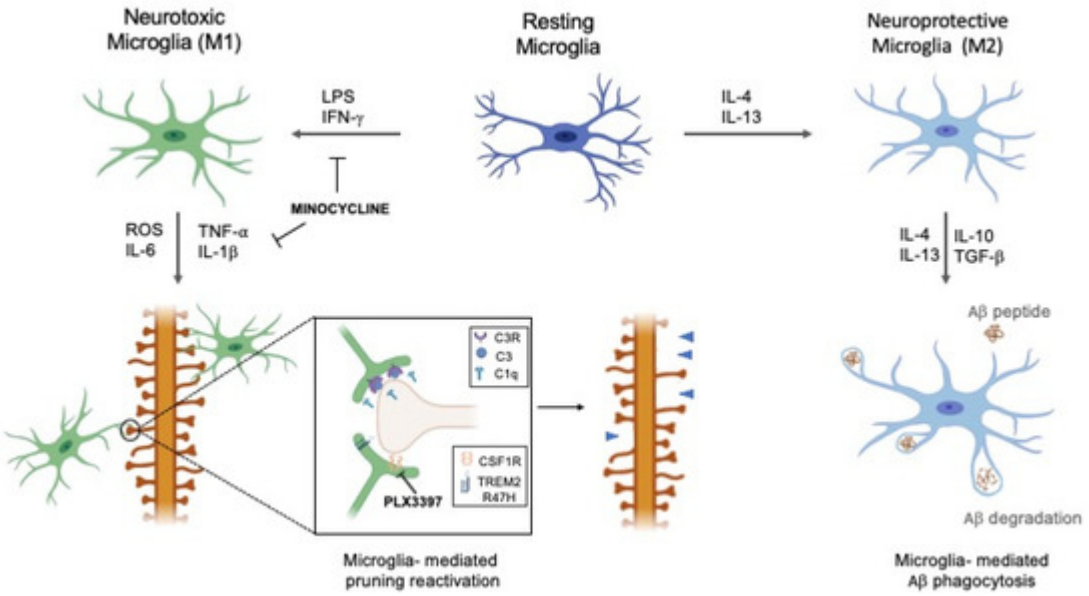

Figure 1. The dual role of microglial phenotypes in Alzheimer’s disease (AD). Depending on the received stimuli, resting microglia can shift to either neurotoxic (M1) or neuroprotective (M2) phenotype. Activated M2 microglia participate in the clustering of amyloid beta (Aβ) plaques and their consequent phagocytosis. Overproduction of pro-inflammatory cytokines by M1 can reactivate microglia-mediated pruning, aided by C1q and C3, leading to pathological synaptic loss. Minocycline can modulate the pathological activation of M1 phenotype and lock the pro-inflammatory mediators’ release, thereby reducing inflammation. The modulation of colony-stimulating factor 1 receptor (CSF1R) and triggering receptor expressed on myeloid cells 2 (TREM2) R47H receptors expressed by

microglia, e.g., through CSF1R inhibitor Pexidartinib (PLX3397) administration, could exert a protective role in preventing microglia-mediated pruning reactivation.

2.2. Microglia in Pathological Conditions

Increasing findings suggest the chronic activation of microglia is a common pathological feature of neurodegenerative disorders characterized by neuroinflammation, such as Alzheimer's disease (AD), Parkinson's disease (PD), and multiple sclerosis (MS).

A central role of microglia in the progression of AD was emphasized by the evidence that misfolded Aβ plaques act as DAMP and thus activate PRRs [29]. Soluble Aβ oligomers and Aβ fibrils bind to several receptors of microglia comprehending CD14, CD36, CD47, α6β1 integrin, class A scavenger receptor, and toll-like receptors (TLRs) [30]. This binding leads to the switch from the quiescent to the active state of microglia which cluster around extracellular plaques, limiting the growth and accumulation of plaques [31].

Therefore, during early stage of AD, clustered microglia has protective effects since it eliminates Aβ plaques, dying or dead cells by its phagocytic activity or by releasing proteases (insulin degrading enzyme, neprilysin, matrix metalloproteinase 9 and plasminogen) [32]. Activated microglia participate in the phagocytosis of Aβ preventing the deposition of Aβ and the formation of amyloid plaques. Microglia clustering plaques for phagocytosis of Aβ has characterized by M2 activation phenotype [33]. Moreover, these macrophages create a physical barrier that prevents plaques spreading [34].

Although early microglia-induced neuroinflammation is a protective response to toxic Aβ, chronic activation may be harmful. An increase in number and size of Aβ plaques results in the dysfunction of microglia in the brain, which is characterized by the overproduction of proinflammatory cytokines leading to synaptic damage. Therefore, the phagocytic activity of microglia is reduced by proinflammatory cytokines, like as IFN-γ, IL-1β, and TNF-α that shift microglia into the pro-inflammatory M1 phenotype [35] contributing to neurotoxicity and synapse loss. As described previously, microglia play a role in complement-mediated synaptic pruning; therefore, a reactivation of this mechanism could drive the progression of neurodegenerative diseases associated with synaptic loss [5] (Figure 1).

In this context, a promising therapeutic strategy could be to modulate microglial activity, promoting neuroprotective phenotype, and attenuating neurotoxic inflammatory stimuli [36]. Minocycline has been widely studied in recent years for its novel mechanism of action. Even if it is a semisynthetic long-acting second-generation tetracycline that is classically active against gram-negative and gram-positive bacteria through inhibition protein synthesis, minocycline is emerging as a potent anti-inflammatory, antiapoptotic, and neuroprotective drug in models of neurodegenerative diseases [37]. Minocycline has a dual mechanism by which could reduce cerebral inflammation and subsequent neuronal loss. It reduces the activation of pro-inflammatory microglial phenotype (M1) and decreases microglial production of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α) and neurotrophic factors (nerve growth factor, NGF) induced by Aβ [38]. In conclusion, minocycline is able to reduce inflammation in

neurodegenerative diseases modulating the pathological shift of microglia and the consequent production of pro-inflammatory responses.

Additionally, microglia cells seem to guide the pathogenesis of AD by active interaction with neurons, astrocytes and oligodendrocytes. Through secretion of IL-1α, TNF-α and C1q, activated microglia leads to the genesis of reactive astrocytes. These distorted cells, called A1 astrocytes, lose the ability to promote neuronal survival, outgrowth, synaptogenesis, and phagocytosis, and induce death of neurons and oligodendrocytes during disease. Using knockout mice lacking microglia, astrocytes failed to activate A1s, showing as reactive microglia are required to induce A1 reactive astrocytes in vivo [39].

In conclusion, even if microglia cells are necessary to immune response in the CNS, protracted microglia polarization is involved in the progression of neurodegenerative diseases.

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