Microglia in Brain Homeostasis and Neuroinflammation

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Neuroinflammation is a common hallmark in different neurodegenerative conditions that share neuronal dysfunction and a progressive loss of a selectively vulnerable brain cell population. Alongside ageing and genetics, inflammation, oxidative stress and mitochondrial dysfunction are considered key risk factors. Microglia are considered immune sentinels of the central nervous system capable of initiating an innate and adaptive immune response. Nevertheless, the pathological mechanisms underlying the initiation and spread of inflammation in the brain are still poorly described.

Keywords: extracellular vesicles ; neurodegenerative disorders ; DAMPs

1. Introduction

Neuroinflammation can be defined as a primary defensive response of the brain against noxious stimuli that compromise the central nervous system (CNS) homeostasis [1]. An initial inflammatory response induces beneficial effects by promoting tissue repair and removing cellular debris. However, the beneficial outcomes can progress to deleterious consequences when chronic inflammation persists, inhibiting the cellular capacity to regenerate. The inflammatory response can endure due to endogenous factors, including genetic mutation or protein aggregation, or be triggered by environmental factors, including infection, trauma and drugs, and can lead to neurodegeneration [1]. Alterations in the microenvironment of the CNS, as in neurodegenerative disorders, can trigger an activation of the microglia and, thus, affect the development of neuronal networks and hasten the progress of the disease. The neuroinflammatory state linked to neurodegeneration induces the sustained release of pro-inflammatory molecules, which results in synaptic dysfunction, neuronal death and neurogenesis inhibition, leading to damage exacerbation [2]. In this sense, neuroinflammation tends to be a chronic process in which the persistence of nefarious stimuli is considered a driving force in the development of the neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS), among others [3][4][5].

Inflammation comprises a complex crosstalk between the brain and infiltrating peripheral immune cells and is characterised by the production of (a) pro-inflammatory cytokines, namely, interleukin-1 beta (IL-1β), interleukin-6 (IL-6), interleukin-18 (IL-18) and tumour necrosis factor (TNF); (b) chemokines, including C-C motif chemokine ligand 1 (CCL1), CCL5 and C-X-C motif chemokine ligand 1 (CXCL1); (c) small-molecule messengers, such as prostaglandins and nitric oxide (NO); and (d) reactive oxygen species (ROS), by innate immune cells in the CNS [6] The chronic neuroinflammation is mediated by non-neuronal glial cells, including activated microglia and reactive astrocytes [7][8][9].

2. The Role of Microglia in Brain Homeostasis and Neuroinflammation

Microglia cells are ubiquitously distributed in the brain, functioning as the main innate immune cells with a key role in the initial response to pathological insults. The main functions of microglia include (a) surveillance of the surrounding environment in the CNS; (b) acting as physiological housekeepers, migrating to injured sites, remodelling synapses and preserving myelin homeostasis; (c) protecting against nefarious stimulus, such as pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), which are described in detail below [10]. During non-physiological conditions, including recognition of foreign pathogens or other adverse stimuli, microglia are activated aiming to restore CNS homeostasis through the alteration in their secretory profile, morphology and phagocytic activity [11][12][13]. On the other hand, chronic inflammation can be triggered or maintained when a pro-inflammatory state in microglia is continuously activated, such as in response to primary neurodegeneration, axonal degeneration and processes linked to macrophages-mediated systemic inflammation [14][15][16].

In response to stimuli, activated microglia upregulate inducible nitric oxide synthase (iNOS) expression and the release of micromolar amounts of NO, and also cause the upregulation of NADPH oxidase (NOX) enzymes and subsequent intracellular ROS formation [17][18]. Under normal conditions, iNOS is not expressed in the brain. However, it can be detected in astrocytes and microglia in response to pro-inflammatory cytokines and pathogen components, including

lipopolysaccharide (LPS), promoting neurodegeneration [19][20]. For several years, it was postulated that from a resting state, microglia can be polarised in two directions. The classical activation of microglia was known as M1 state, in which pro-inflammatory responses are predominant. An alternative microglial activation was known as M2, mainly responsible for resolution and repair, and represents an anti-inflammatory phenotype [21][22][23].

While M1 microglia polarisation was characterised by an increase in the expression of pro-inflammatory molecules, M2 microglial activation was further divided into four subtypes, M2a, M2b, M2c and M2d [24][25]. The M1 phenotype was characterised by several markers of cell surface, including CD11b, CD16, CD32 and CD86, and displays the pro-inflammatory response by expressing IL-1β, IL-6, IL-8 and TNF-α [26][27]. On the other hand, the M2 phenotype was characterised by other cell surface markers, including CD206, CD163 and arginase, and induces pro-inflammatory responses by expressing IL-10, IL-4, IL-13 and TGF-β [25][28].

The M1–M2 paradigm of microglial activation is artificial and only convenient to simplify the research in the field; currently, it is considered an oversimplified model that does not reflect the microglia complexity [29][30][31]. Accordingly, several microglia functions have been attributed considering their reaction through different phenotypes that are associated with distinct molecular signatures [32][33]. Moreover, microglia subtypes might display diverse intrinsic properties acquired during maturation or as a consequence of functional specialisations within the CNS. The coexistence at steady state of these subtypes allows them to undergo further modulation or phenotypic transformation in response to different *stimuli* [25][33][34]. Microglia might constitute a community of cells in which different members have several properties performing distinct physiological functions and responding differently to a particular stimulus [33][35]. The heterogeneity of microglia is related with several aspects, including temporospatial and gender-related differences regarding cellular origin, colonisation, abundancy, morphology, mobility (i.e., migration) and motility (extension and/or retraction of the processes), as well as gene expression, all of which ultimately reflect into diverse physiological and pathological functions [36]. The microglia morphology can be different in the presence of neuronal cell bodies, dendrites and axons, myelinated axons and blood vessels [32][35][37][38]. Under normal physiological conditions or after a stimulus (e.g., LPS), microglia show differences in self-renewal and turnover rates [35][38]. Using lipocortin 1 immunoreactivity as a brain-specific microglial marker, Savchenko et al. demonstrated that microglial density was higher in the forebrain, lower in the midbrain and lowest in the brainstem and cerebellum [39]. A more recent study, using time-lapse in vivo imaging, confirmed differences in the distribution and morphology between cerebellar and cortical microglia, with the latter having a higher microglial density and ramification compared to their counterparts [40]. However, the role of such microglia densities heterogeneity across distinct regions or even in the same region of the CNS remains unclear.

In most brain regions, microglia cells have a normal ramified morphology with extended branches, although significant variation in that morphology has been identified [41][42]. Vela et al. investigated the morphology and distribution of microglia in normal cerebellum of both young and adult mice through histochemical assays with nucleoside diphosphatase, a microglial marker. Importantly, this study demonstrated that microglia could have different sizes and ramification patterns not only within the same layer but also between different histological layers of the cerebellar cortex [42]. In summary, microglia, as a heterogeneous community of cells, can acquire different phenotypes which compromise important functional properties. These distinct subpopulations can coexist in the same brain structures and generate a non-uniform inflammatory response.

Strong evidence suggests that microglia are key regulators of inflammatory responses in neurodegenerative disorders, such as AD, PD, HD and ALS, among others. The distinctive neuroinflammatory state of these diseases promotes the continuous release of pro-inflammatory molecules that results in synaptic dysfunction, neuronal death and inhibition of neurogenesis, creating a vicious circle that exacerbates the damage [2]. Recently, a comprehensive single-cell RNA analysis of brain immune cells revealed disease-associated microglia (DAM) in the context of AD [43]. Several studies have since demonstrated the existence of neurodegenerative disease-associated phenotype of reactive microglia in AD, ALS and Frontotemporal Dementia (FTD) defined by a unique transcriptional and functional signature [43][44][45][46]. Most of these gene expression profiles were found in human genome-wide association studies (GWAS) associated with AD and other neurodegenerative disorders [19][43][47]. The DAM program is related to the expression of a subset of genes, such as TREM2 (triggering receptor expressed on myeloid cells 2), essential for its activation. In fact, studies using mouse models of neurodegenerative diseases deficient for TREM2 revealed that TREM2 signalling is essential for microglia to detect and respond to the “neurodegeneration cues”. TREM2 loss of function on microglial gene expression is associated with an increased risk for several neurodegenerative conditions, including AD, PD, ALS and FTD [48][49][50][51][52]. In *postmortem substantia nigra* and *putamen* brain tissue of sporadic PD, TNF-α, IL-1β, IL-6 and interferon-γ (IFN-γ) mRNAs levels are increased when compared to healthy controls [53][54]. In addition, in 6- hydroxy-dopamine (6-OHDA) treated mice, anti-inflammatory molecules, such as IL-10, were decreased, while pro-inflammatory cytokines, including IL-1β, IL-6, TNFα and IFN-ɣ, were upregulated [55]. TNF-α is highly expressed in dopaminergic neurons from PD patients and can exert a

deleterious effect during an inflammatory response, such as triggering apoptotic cell death [56]. In rat hippocampal neurons, IL-1β treatment for 24 h (3 ng/mL) induces synaptic loss, depending on the simultaneous activation of both pre- and post-synaptic pathways [57]. A recent study using RNA sequencing analysis of microglia from mouse models for neurodegenerative disorders, namely, $App^{NL\text{-}G\text{-}F/NL\text{-}G\text{-}F}$ (AD), rTg4510 (tauopathy) and $SOD1^{G93A}$ (ALS) mice, demonstrated a reduction in the homeostatic microglial genes, whereas the DAM-associated genes were upregulated when compared to wild type (WT) [58]. In the same study, the gene expression of microglia-specific markers in *postmortem* brain tissue of early AD patients was also decreased, although the expression of DAM-related genes was not upregulated [58]. In the context of AD, another study demonstrated that the cerebral microcirculation participates in the inflammatory process as mediator. In fact, AD patients' brain microvessels release higher levels of pro-inflammatory cytokines, such as TNF-α, IL-1β and IL-6, even under basal conditions, when compared to healthy control brains [59]. Importantly, anti-inflammatory cytokines, including IL-1 receptor antagonist, IL-4, IL-10 and IL-11, are also produced during the neuroinflammation process and could be part of a sophisticated mechanism to counteract excessive neuroinflammation [60][61][62]. In this sense, cerebrospinal fluid (CSF) from AD patients showed higher levels of pro-inflammatory, as well as anti-inflammatory cytokines, including eotaxin, IL-1ra, IL-4, IL-7, IL-8, IL-9, IL-10, IL-15, granulocyte colony-stimulating factor (GCSF), monocyte chemotactic protein 1 (MCP1), TNF-α and platelet-derived growth factor [63]. Importantly, a negative correlation between disease progression and the levels of several cytokines, such as IL-1β, IL-4, IL-6, IL-9, IL-17A, basic fibroblast growth factor, MCP1, IFN-γ and macrophage inflammatory proteins-1β was reported in the same study [63]. These effects might be dependent on the NLRP3 inflammasome activation since NLRP3 knock-out (KO) APP/PS1 mice for NLRP3 demonstrated decreased caspase-1 and IL-1β levels in the brain, enhanced amyloid-β (Aβ) clearance and were largely protected from spatial memory loss. Importantly, the microglia from those mice were switched to an anti-inflammatory phenotype (M2), promoting a decrease in Aβ levels [64]. The brain autopsy of multiple sclerosis patients evidenced a decrease in the microglial expression of Purinergic Receptor P2Y12 (P2RY12), a homeostatic microglial marker, as well as a higher susceptibility to a more pro-inflammatory phenotype, including the expression of phagocytic-related markers (macrosialin), antigen presentation markers (MHC class I and II molecules and T lymphocyte activation antigen CD86) and proteins involved in the production of ROS (cytochrome b-245 light chain) [65].

Although it seems clear that different microglia phenotypes are involved in physiological and pathological processes, the mechanisms involved in the regulation/activation of those different phenotypes remain unknown. It is likely that different phenotypes may be switched on by different triggers. In the context of neurodegenerative disorders where mitochondrial dysfunction is, alongside inflammation, one of the main hallmarks, it is conceivable that neuroinflammation could be mediated by released pro-inflammatory components by mitochondria. Thus, further studies are warranted to investigate not only the involvement of the different microglia phenotypes in physiological and pathological processes, such as neuroinflammation, but also to better understand how microglia respond to DAMPs through the expression of various immune receptors, including chemokine and pattern recognition receptors (PRRs), contributing to a gradual loss of neuronal function.

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