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Astrocytes play critical roles in neuroinflammation and Parkinson's disease

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Parkinson's disease (PD) is a multifactorial disorder characterized mainly by the loss of dopaminergic neurons in the substantia nigra of the brain. The pathogenesis of a spontaneous PD is suggested to be multifactorial, an aberrant immune function being one of the factors influencing PD-associated neurodegeneration. It was found that negrostriatal astrocytes get involved in this process. Astrocytes play vital roles in brain homeostasis as well as participate in the local innate immune response triggered by a variety of insults. Astrocytes are not immune cells, but when sensing injury-associated molecular patterns they transform through a process called "reactivity" and become important regulators of the immune response. However, the underlying molecular mechanisms of astrocytes' contribution to the PD-associated neurodegeneration are not fully understood. A better understanding of astrocyte functions in PD may provide insights into PD pathogenesis and novel therapeutic approaches for the disease. This paper reviews the role of astrocytes in innate immunity and PD.
Key words: astrocytes; neuroinflammation; Parkinson's disease.

INTRODUCTION

Parkinson's disease (PD) is a neurodegenerative disorder best characterized by the death of dopaminergic (DAe) neurons in the *substantia nigra* (SN), a basal ganglia structure located in the midbrain. The pathogenesis of spontaneous PD is thought to be multifactorial, deriving from environmental factors that act on genetically predisposed aging individuals [1]. Recent research has found that the immune system may play a role in the development of this disorder [2]. The immunity of the central nervous system (CNS) is kept in a segregated state, with a marked partition existing between the brain parenchyma and meningeal spaces. While the brain parenchyma is patrolled by microglia, perivascular and meningeal macrophages mediate immune responses at brain boundaries [3]. Unlike microglia, astrocytes are not immune cells, but when sensing injury-associated molecular patterns they change through a process called "reactivity" and become essential regulators of the adaptive and innate immune response [4, 5]. Moreover, recent evidence reveals that astrocytes may have a "molecular memory" of previous reactivity events [6]. This review will address the currently available evidence on the role of astrocytes in innate immunity and PD.

Astrocytes play a critical role in maintaining brain tissue homeostasis

Astrocytes are the predominant type of glial cells in the CNS, usually identified by their stellar shape and expression of glial fibrillary acidic protein (GFAP). Astocytes amount to approximately 30% of the total number of brain cells. They are derived from the neuroepithelium of the developing CNS. Microglial cells, in sharp contrast, originate from the yolk-sac, a mesoderma-related structure [7]. In the postnatal brain mature astrocytes can re-enter the cell cycle and proliferate [8].

Astroglial cells serve a number of vital roles. They provide biochemical support for

endotheliocytes to form the blood-brain barrier (BBB), assist in maintaining ion balance, participate in the regulation of local blood flow and provide a multifaceted support to neurons [9, 10]. Extensive cellular processes of astrocytes contact both synapses and microvessels making these cells a functional bridge from neurons to blood flow. In particular, they link elevations in neuronal activity to increases in blood flow through a process called neurovascular coupling. Astrocytes influence the microvasculature by releasing vasoactive substances and pro-angiogenic cytokines [10, 11].

Being connected together with gap junctions individual astroglial cells form a syncytium. Intracellular connectivity enable them to transfer ions and molecules to neurons that may reside at a distance from the blood capillary. Astrocytes provide neurons with energy substrates (e.g., lactate), and antioxidants (e.g., glutathione) required for scavenging reactive oxygen species (ROS). The synthesis of glutathione in neurons is dependent on astrocytes. Extracellular cysteine, the precursor, is readily auto-oxidized to cystine preventing its uptake by neurons that lack a cystine transport system. Astrocytes take up cystine, reduce it to cysteine and release the latter back into the extracellular space. This cysteine is finally taken by neighboring neurons and used for glutathione synthesis [12]. Astrocytes secrete metallothioneins, cysteine-rich proteins, possessing radical-scavenging properties [13]. Even more importantly, astrocytes release neurotrophic factors promoting neuronal survival and plasticity [14].

It is worth to note that astroglial cells remove and recycle potentially toxic glutamate, the main excitatory neurotransmitter in the CNS. Released in the synaptic cleft the latter is taken up through Na^+-dependent excitatory amino acid transporters (EAATs), which are predominantly expressed in astrocytes [15]. Astrocytic processes ensheathing synapses feature neurotransmitter receptors. When activated these receptors trigger Ca^{2+} release from the endoplasmic reticulum. Then, through gap junctions Ca^{2+} can spread to neighboring astrocytes and influence the activity of nearby neurons [16].

Aforementioned functions of astrocytes entail their specific arrangement in the brain tissue. These cells are rare in areas with a high density of neuronal cell bodies, being replete in areas full of dendrites and axons [17]. Typically, astrocytes reside within clearly defined regions. Their location is determined in embryonal period and change little during postnatal life [18]. Thus, astroglial cells may act as stable repositories of spatial information necessary for the development and local regulation of brain functions.

Astrocytes are important effectors of innate immunity in the CNS

Together with microglia, astrocytes play an important role in innate immunity. Usually, immune responses in the CNS are isolated from similar events at the periphery. In pathology, however, both microglia and astrocytes can engage in a cross-talk with CNS-infiltrating immunocytes providing, among other things, the informational input for adaptive immunity [19]. They use pattern-recognition receptors to detect the presence and nature of pathogens. Astrocytes display an array of such receptors, including Toll-like receptors (TRLs), nucleotide-binding oligomerization domains, double-stranded RNA-dependent protein kinase, scavenger receptors, mannose receptor and components of the complement system [20].

When pathogens are recognized by TLRs they evoke activation of NF-κB, a transcription factor, resulting in increased transcription of genes encoding IL-1 family cytokines [21]. Release of these proinflammatory cytokines depends on caspase-1 initiated by signaling from another set of receptors, termed “nucleotide-binding domain leucine-rich repeat-containing receptors” (NLRs), whose function is, in turn, dependent on the assembly of inflammasomes [22].

NLRs can be activated, for example, by aggregated peptides or ATP released from

damaged cells. Cooperative TLR- and NLR-related signaling leads up to secretion of IL-1 family cytokines [23]. Both receptor families are expressed in microglial and astroglial cells. However, astrocytes feature a more restricted array of the receptors [24].

In response to CNS injury, astrocytes turn into reactive ones. The intensity of this transformation, which includes GFAP upregulation, varies depending on the severity of an injury [25, 26]. More specifically, reactive astrocytes are induced by cytokines secreted by activated microglia [27]. Reactive astrocytes are often morphologically distinct from 'resting' ones being larger and more ramified. They can be further classified into neurotoxic and neuroprotective ones [28]. The former lack phagocytic capacity, exhibit Ca^{2+} dysregulation, release numerous proinflammatory cytokines and chemokines, ROS and fail to uptake glutamate [29].

Neuroprotective astrocytes, in contrast, secrete an array of factors aiding synaptic development, repair and rewiring, e.g., TGF-β, IL-33, BDNF [30]. They also assist microglia in clearing debris and/or protein aggregates. However, this binary classification of reactive astrocytes has been recently challenged by single-cell transcriptomics data [31].

Mediators released by astrocytes trigger two basic types of events: they activate neighboring cells amplifying the local innate immune response and modify BBB permeability allowing peripheral immunocytes to enter the brain tissue. In health, the BBB assists in restraining CNS inflammation by excluding plasma proteins as well as peripherally derived immune cells. A healthy CNS environment is anti-inflammatory, featuring high concentrations of such cytokines as TGF-β and IL-10 as well as gangliosides, which can be toxic to T cells [19].

Astrocyte-derived factors activate microglia and regulate its migration and proliferation [20]. In particular, chemokines (CCL2 and CXCL12) promote the recruitment of inflammatory immune cells into the CNS and have a role in attracting neural progenitors closer to areas of brain injury [32]. In addition, reactive astrocytes promote BBB repair and support neuronal survival [33].

Astrocytes themselves can be direct targets of chemokines and cytokines. Astrocytic responses to the former involve chemotaxis, cell proliferation and survival. Chemokines (e.g., CXCL12 and CCL5) induce glutamate release as well as the synthesis of cytokines and chemokines. Cytokines TNF, IFNg and IL-1 are major astrocytic activators. It is interesting that astrocytes are resistant to death receptor-induced apoptosis what helps them to survive inflammatory insults [34]. However, their functions may be compromised during inflammatory reactions. High levels of TNF-α produced by microglia impair the capacity of astrocytes to remove glutamate leading to excitotoxicity [35]. Astrocytes and microglia, together, restrict the lesioned area by the formation of scar tissue. In result, an inflammatory response occurs within this clearly demarcated area [36].

It may be concluded that astrocytes react to an injury with a unique activation program that modulates or amplifies the local inflammatory reaction. On the one hand, they can promote inflammation. On the other hand, proliferating reactive astrocytes confine lesions and restore brain homeostasis. The balance between pro- and anti-inflammatory pathways is fundamental for controlled reactions to CNS trauma. Microglial-astrocyte interactions are critical in CNS innate immunity.

Astrocytes play important roles in Parkinson's disease

PD is a multifactorial disorder characterized mainly by the loss of DAe neurons in the SN of the brain. PD neurodegeneration is usually accompanied by accumulation of α-synuclein, a protein that normally regulates synaptic vesicle trafficking [37]. Although the mechanism of PD neurodegeneration remains a matter of discussion, various pathogenic factors are

thought to be in play, an aberrant immune function being among them [38].

Accumulation of reactive astrocytes in the brain, especially in affected areas, is typical of neurodegenerative diseases. Post-mortem studies of PD brains have identified mild increases in astrocyte numbers and GFAP-immunoreactivity in the SN [39]. In contrast, the astrogliosis was dramatic in the brains of several parkinsonian models. Animals injected with 6-hydroxydopamine (6-OHDA) or 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) exhibited prominent increases in astrocyte numbers and GFAP-immunoreactivity in the striatum and SN [40, 41]. The intracerebral rotenone infusion also caused a marked increase in astrocyte density in the SN of the rat brain [42, 43]. The density of GFAP-positive cells correlated strongly with the intensity of neuronal injury in PD brains [44].

These PD-related changes of astrocytes reflect the general dynamics of the neuroinflammatory process. The latter also manifests itself in increased levels of pro-inflammatory cytokines observed in the cerebrospinal fluid of PD patients [45] and in the SN of PD brains [46, 47]. Inflammation promotes DAe degeneration as shown by the intranigral injection of lipopolysaccharide [48]. Supportive evidence was provided by DAe neurotoxicity observed in transgenic mice expressing TNF-α specifically in the brain [49]. On the other hand, neuroprotective effects were reported when preventing astrocytic NLRP3 inflammasome activation and subsequent IL-1β production [50, 51].

α-Synuclein inclusions are regarded the hallmark of sporadic PD. The fibrillar form of this protein, aggregated and insoluble, constitutes a major component of Lewy bodies found in neurons [52]. Normally, neurons can release cytosolic α-synuclein into the extracellular space, from where it can be endocytosed by astrocytes [53]. These cells can further degrade α-synuclein via proteasome and autophagy pathways [54]. The accumulation and deposition of this protein in astrocytes can stimulate the production of proinflammatory cyto- and chemokines. This response is dependent on TLR4 [55]. Interestingly, the number of SN astrocytes containing α-synuclein inclusions positively correlates with the severity of DAe neuronal loss in this brain region [56].

Cu accumulates in the aging brain and its binding to α-synuclein can initiate aggregation of the protein [57]. It was shown that metallothioneins bind Cu with a high affinity being capable to prevent Cu-related aggregation of α-synuclein [58]. Recently, it was observed that overexpressing of metallothioneins in PD brains may influence α-synuclein aggregation [59].

Nuclear factor erythroid 2-related factor 2 (Nrf2) is a transcription factor present mainly in astrocytes where it induces the expression of various antioxidant genes [60, 61]. The activation of Nrf2 signaling pathway stimulates the production of antioxidants in neighboring neurons, while its disruption leads to the opposite effect. Nrf2 knockout mice showed exacerbated gliosis and DAe neurodegeneration after MPTP injection [62].

DJ-1, a redox-sensitive protein, is mainly expressed in astrocytes where it acts as a sensor of oxidative stress [63, 64]. Reactive astrocytes inhance DJ-1 expression and release the protein into the extracellular space [65]. DJ-1 gene deletions and point mutations have been identified as one of the causes of early-onset autosomal recessive PD [66]. Evidence suggests that DJ-1 stabilizes the transcriptional regulation of Nrf2 [67]. Moreover, DJ-1 selectively influences TLR4 to regulate astrocytic activities related to inflammation. DJ-1 deficient astrocytes produce pro-inflammatory mediators, such as COX-2 and IL-6 [68]. In addition, DJ-1 deficiency alters the expression of EAAT2 impairing glutamate uptake by astrocytes and leading to excitotoxicity [69]. DJ-1 deficiency led to glial activation and DAe neurons' death in the SN of the murine brain [70].

In health, astrocytes play a pivotal role in BBB maintenance by releasing TGF-α and

GDNF that influence tight junction formation in endothelial cells [71]. An increased permeability of the BBB in the putamen of PD patients was found to be related to the loss of normal astrocyte function [72].

Existing evidence indicates that the dysfunction of the autophagy-lysosome pathway in astrocytes may be implicated in PD pathogenesis. PINK1, a serine/threonine-protein kinase, builds up on the outer mitochondrial membrane and recruits a protein named parkin. The PINK1/parkin pathway then designates the mitochondria for degradation by lysosomes. Mutations in the PINK1 gene cause a form of autosomal recessive early-onset PD. The loss of PINK1 increases levels of iNOS, NO, TNF-α, and IL-1β in astrocytes under neuroinflammatory conditions [73]. The dysfunction of PINK1-parkin-mediated mitophagy in astrocytes can disrupt mitochondrial maintenance [74].

Leucine-rich repeat kinase 2 (LRRK2), also known as PARK8 is a large, multifunctional enzyme interacting with the parkin. It is also a substrate for chaperone-mediated autophagy. LRRK2 is constitutively expressed in neurons and glial cells in the human brain [75]. Astrocytic LRRK2 as well as neuronal one are involved in the autophagy-lysosome pathway [76]. Mutations within LRRK2 gene alter autophagy and lead, consequently, to α-synuclein accumulation [77]. These mutations cause the development of autosomal-dominant PD [78].

Parkin (PARK2), an E3 ubiquitin ligase, forms a complex with PINK1 and DJ-1, and by ubiquitination promotes the degradation of misfolded proteins. In particular, upon cellular insult parkin recognizes proteins on the outer membrane of mitochondria and mediates the clearance of damaged mitochondria via autophagy [79]. Constitutive parkin expression is higher in neurons than in astrocytes. However, astrocytes increase parkin expression during the response to unfolded proteins [80]. Parkin deficiency was found to impair glutathione synthesis in astrocytes making DAe neurons vulnerable to oxidative stress [81].

CONCLUSIONS

In conclusion it can be said that astrocytes are deeply involved in the PD pathogenesis. The response a brain tissue to DAe neurons' death includes an inflammation that starts developing as a protective reaction. However, a high level of neuroinflammation can negatively influence the extent and rate of death of DAe neurons. Astrocytes are important effectors of innate immunity and regulators of innate and adaptive immune responses. Influencing the intensity of neuroinflammation, i.e., switching astrocytes from neurotoxic to neuroprotective subtypes, may have an effect on the disease dynamics. Studying the mechanisms of astrocyte involvement will help to find means to counteract the degeneration of DAe neurons.

The author of this study confirm that the research and publication of the results were not associated with any conflicts regarding commercial or financial relations, relations with organizations and/or individuals who may have been related to the study, and interrelations of author of the article.

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АСТРОЦИТИ ВІДІГРАЮТЬ ВАЖЛИВУ РОЛЬ У НЕЙРОЗАПАЛЬНИХ ПРОЦЕСАХ І ХВОРОБІ ПАРКІНСОНА

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Хвороба Паркінсона (ХП) є багатофакторним захворюванням, що характеризується насамперед втратою дофамінергічних нейронів у чорній субстанції головного мозку. Вважається, що патогенез спонтанної ХП багатофакторний, а аномальна імунна функція є одним із факторів, що впливають на нейродегенерацію, асоційовану з ХП. Встановлено, що в цьому процесі беруть участь астроцити чорної субстанції. Астроцити відіграють життєво важливу роль у гомеостазі мозку, а також у локальних реакціях вродженого імунітету, викликаних дією різноманітних факторів. Вони не є імунними клітинами, але під впливом молекулярних сигналів, що пов'язані з пошкодженням, трансформуються у процесі, який називають "реактивністю", і стають важливими регуляторами імунної відповіді. Однак основні молекулярні механізми внеску астроцитів у пов'язану з ХП нейродегенерацію залишаються недостатньо вивченими. Краще **розуміння** функцій астроцитів

при **ХП** може поглибшити **розуміння** патогенезу **ХП** та допомогти у розробці нових терапевтичних підходів. У цій статті представлений огляд сучасних даних щодо ролі астроцитів у реакціях вродженого імунітету та механізмах розвитку ХП.

Ключові слова: астроцити; нейрозапалення; хвороба Паркінсона.

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