Astrocytes in Multiple Sclerosis

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In multiple sclerosis (MS), astrocytes respond to the inflammatory stimulation with a robust process of morphological, transcriptional, biochemical and functional remodeling. Recent studies exposed the detrimental and the beneficial, in part contradictory, functions of this cell population. The pivotal roles played by astrocytes make them an attractive therapeutic target. Improved understanding of astrocyte function, diversity, and the mechanisms by which they are regulated, may lead to the development of novel approaches to selectively block astrocytic detrimental responses and/or enhance their protective properties.

Keywords: astrocytes ; multiple sclerosis (MS) ; experimental autoimmune encephalomyelitis (EAE) ; inflammation ; astrocyte activation ; blood–brain barrier (BBB) ; tissue damage ; neurotrophic factors ; neuroprotection ; repair processes

1. Introduction

Multiple sclerosis (MS) is a complex disease of the central nervous system (CNS), in which the pathological process combines autoimmune inflammation, demyelination, and neurodegeneration [1]. Cross-talks between penetrating immune cells and resident cells are involved.

Astrocytes (astroglia), the most abundant cell type in the CNS, are versatile dynamic cells, expressing numerous receptors, which enables them to respond to neuroactive compounds, such as neurotransmitters, neuropeptides, growth factors, cytokines, and toxins [2]. With their highly ramified processes that contact the neurons' pre- and post-synaptic terminals, astrocytes regulate synaptic formation, activity, and plasticity [3]. Astrocytes provide energy substrates and trophic factors for neurons and oligodendrocytes, and maintain the extracellular milieu composition, pH, and electrolyte balance via specialized water and ion channels [2][4]. They also control the neuronal microenvironment by secreting or removing active factors, which trigger receptors on neurons, glia, and blood vessels [2]. Lipid metabolism is also mediated by astrocytes, which are the primary source of CNS cholesterol, needed for membrane and myelin synthesis [5].

Astrocytes are key components for the functionality of the blood brain barrier (BBB), and the glia-limiting membrane (glia limitans) of the meningeal brain barriers, which control the entry of molecules and cells into the brain parenchyma [6]. By extending and wrapping their endfeet around the cerebral vasculature, perivascular astrocytes exchange glucose, ions, and soluble factors with the endothelial cells, regulating neuronal metabolism [7][8]. Several studies indicate that astrocytic branches can sense neuronal synaptic activity levels, integrate this information, and transmit it to adjacent blood vessels [9][10]. The neuro–hemodynamic coupling role of astrocytes is further supported by the finding that astrocytes, rather than blood vessels, show a striking morphological homology to the neuronal functional boundaries [11].

In parallel to the advance in understanding astrocytes' contribution to brain function and homeostasis, their activity under pathological circumstances, particularly in MS, was investigated. Studies, utilizing novel technologies in MS patient samples, and in the animal model of MS, experimental autoimmune encephalomyelitis (EAE), have revealed the detrimental and the protective roles of this multifaceted cell population in facilitating inflammation, tissue damage, and repair.

2. Astrocyte Mediators of MS Pathology and Regulation

Astrocytes on the CNS borders, as well as in the lesion sites where they comprise the most prevalent cell type, play detrimental roles in various critical points of MS pathogenesis, constructing inflammatory cascades and inflicting tissue injury. Under inflammatory conditions reactive perivascular astrocytes retract their processes and detach from the blood vessels [12] resulting in BBB breakage and massive infiltration of immune cells into the CNS. Astrocytes also "actively" recruit leukocytes into the CNS parenchyma by producing chemoattractant molecules and inducing an increased

expression of adhesion molecules on the endothelial cells [6][13][14]. Furthermore, astrocytes create a hostile environment, rich in pro-inflammatory and toxic factors that inflict damage to myelin, oligodendrocytes, and neurons, by various routes [14].

Conversely, the roles of astrocytes in restricting the detrimental inflammation have also been established. Reactive astrocytes employ a variety of strategies to counteract the inflammation, limit BBB and tissue damage, and support repair neuroprotective processes, thus contributing to disease arrest and to recovery of CNS functions [15][16]. Furthermore, in response to CNS insults, astrocytes receive and carry information to other cells, in a coordinated action to stimulate defense and repair mechanisms [17].

3. Astrocytes as A Therapeutic Target—Modulation of Reactive Astrocytes by MS Treatments

The pivotal roles played by astrocytes make them an attractive target for MS therapy. None of the currently approved MS treatments specifically target astrocytes, but effects on astrocytes have been demonstrated for several therapies such as dimethyl fumarate (DMF) [18][19] Fingolimod [20] Laquinimod [21] interferon (IFN)-β [22] and glatiramer acetate (GA) [12][23][24].

Ideally, astrocyte-directed treatments should take into account their multi-functionality, and attempt to block detrimental responses while enhancing protective properties. The current notion that astrocytes are heterogeneous with respect to the molecules they express and the functions they exhibit, raises the possibility to manipulate specific astroglial populations. Several novel approaches to affecting astrocytic beneficial properties were recently suggested. Stimulation of metabotropic glutamate receptors (mGluR), in particular mGluR3 and mGluR5, which are upregulated in reactive astrocytes, elicits neuroprotective repair processes such as astrocytic BDNF synthesis [25]. Metabolites of dietary tryptophan, produced by the commensal flora, control TGF-α and VEGF-β production, resulting in the modulation of the astrocytic transcriptional program and CNS inflammation [26]. The detection of a metabolic control mechanism that drives pro-inflammatory astrocyte activities through the mitochondrial antiviral signaling protein (MAVS), may lead to identification of new therapeutic targets [27]. Furthermore, a subset of astrocytes expressing the lysosomal protein LAMP12 and the death receptor ligand TRAIL3, which limits CNS inflammation by inducing T-cell apoptosis, has been recently identified [28]. These astrocytes are maintained by meningeal IFN+ NK cells, in which IFN-γ expression is modulated by the gut microbiome, suggesting a novel mechanism for astrocyte modulation. Selective regulation of the diverse astrocyte activities requires further knowledge of their subset heterogeneity and plasticity, as well as deeper understanding of their activation signaling.

4. Conclusions

While the pathological inflammatory process in MS/EAE is primarily initiated by bone-marrow-derived components, it is currently clear that astrocytes play essential roles in recruiting, instructing, and retaining these leukocytes at the lesion sites, engendering the positive-feedback inflammatory loop that mediates the disease. Astrocytes also inflict tissue damage through their intrinsic neurotoxic activities and the activation of other cells, thus promoting neurodegeneration and disease progression. Conversely, the roles of astrocytes in restricting detrimental inflammation and in promoting neuroprotection and repair have also been established. These combined effects emphasize the importance of astrocytes as fundamental constituents of MS pathology and regulation. Yet, the multiple, in part opposing, functions raise the notion that astrocytes are bystander “flexible” participants tuned by various context-specific factors, such as the region in which they reside, the nature and the severity of the CNS insults, the local pro/anti-inflammatory milieu, and the crosstalk with immune and resident cells. The current focus in astrocyte biology research is on the heterogeneity and the characterization of specific astrocytic subsets. The diversity of astrocytes with respect to the molecules they express and the functions they exhibit is widely appreciated, while their different regulation and activation signals, as well as their plasticity and communication with neighboring cells, are intensively investigated. Improved understanding of astrocyte diversity and the mechanisms by which they are regulated may lead to identification of novel targets to selectively manipulate astrocytic response, for the development of effective MS treatments.

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