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Review

The secretome signature of reactive glial cells and its pathological implications ☆

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ABSTRACT

Glial cells are non-neuronal components of the central nervous system (CNS). They are endowed with diverse functions and are provided with tools to detect their own activities and those of neighboring neurons. Glia and neurons are in continuous reciprocal communication under both physiological and neuropathological conditions, and glia secrete various guidance factors or proteinaceous signals that service vital neuronal–glial interactions in health and disease. Analysis and profiling of glial secretome, especially of microglia and astrocytes, have raised new expectations for the diagnosis and treatment of CNS disorders, and the availability of a catalog of glia-secreted proteins might provide an origin for further research on the complex extracellular signaling mediated by glial cells. Components of the glial secretome play important roles as mediators and modulators of brain structure and function during neuroprotection and neurodegeneration. Therapeutic hypothermia has been acclaimed an effective modulator of brain injury via its substantial effect on the protein expression profiles of glia. Furthermore, emerging proteomic tools and methodologies make feasible the documentation of the reactive glial secretome signature. This review focuses on reactive glial cells and the uniqueness of their secretome during diverse neuropathological conditions. This article is part of a Special Issue entitled: An Updated Secretome.

1. Introduction

The nervous system consists of trillions of glia and neurons that are present in a ratio of ~50:1 [1–5]. Investigation of diverse aspects of neurons, including their properties and the mechanisms that govern the development and functions has been carried out. Glia, which compose a voluminous support system, are essential for the proper operation of the nervous system [6–11]. Although the glial research has undoubtedly gained tremendous progress in recent years, current knowledge on the mediators of glial function is limited. Nonetheless, glia are key players in disorders of nervous system. In fact, the majority of brain malignancies are of glial character or origin [12–16]. Glial defects are also associated with neurodegenerative diseases [17–19], including amyotrophic lateral sclerosis (ALS) [20], Parkinson's disease (PD), and Alzheimer's disease (AD) [21–25]. This suggests that an understanding of glial functions, and how they go awry, is indispensable for comprehending brain functions and dysfunctions. Glia perform a plethora of critical functions in the nervous system. Actually, glial manipulation often results in neuronal loss, which precludes investigations of the effects glia may have on neuronal morphogenesis and activity. Glia are essential for neural development, for example, they promote axon outgrowth, dendrite extension, and the morphological plasticity of neuronal receptive endings [26,27]. Glia respond to environmental stimuli independently of neurons, and some responses may promote neuronal remodeling [28,29]. As mentioned above, glia and neurons are in constant reciprocal communication under both physiological and neuropathological conditions, and thus, glia may interpret extracellular cues to alter neuronal activity [30]. Glial cells talk to each other and neurons predominantly by using secreted proteins, which in the extracellular environment participate in the control and regulation of many biological and pathological processes in the nervous system. For example, neuritogenesis is driven by two main governing forces; internal neuron-derived guidance, and guidance by factors originating from the microenvironment surrounding neurons, and many of these factors are secreted by glial cells.

The glia-derived guidance factors required for neuronal–glial interactions are proteinaceous in nature. Secreted proteins coordinate cell growth, division, differentiation, and apoptosis by acting as intercellular signals in multicellular organisms, and also play key roles in the control and regulation of numerous biological and disease processes, such as, cancer and immune, cardiovascular, and neurodegenerative diseases [31,32]. Interest in secretomics research has multiplied many folds during recent years, because secretomics is believed to have the potential to provide diagnostic and prognostic biomarkers and to

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identify therapeutic targets. Along with the tremendous expansions in proteomic platforms such as mass spectrometry instrumentation, increasing collaboration between biologists, clinicians and analytical chemists may assist in functional investigations of secretome, providing relevancy in terms of a given situation such as disease. A combined and truly multidisciplinary effort is necessary for the generation of a valuable secretome catalogs having diagnostic, prognostic and therapeutic values. Glia, predominantly microglia and astrocytes, provide neurons with nutrients and protection, and are indispensable components of defense mechanisms against pathological events in the CNS [33–36]. Activated glial cells release pro-inflammatory mediators that trigger the activations and proliferations of other glial cells, which if unchecked, can ultimately resulting in the pathological state of neuroinflammation [35,37]. Research findings of the last few of decades provide ample evidence that neuroinflammatory processes play important roles in the pathogenesis of both acute and chronic neurological disorders [38–44].

2. Profiling of glial secretome as a regulator of CNS health and disease

Numerous proteins secreted by glial cells, especially microglia and astrocytes, reflect a broad variety of glial conditions in the CNS, including neuroinflammation and have neuroprotective and neurotoxic effects [45]. Glia-secreted proteins play critical physiological and pathological roles in the nervous system, and the proteomic signatures of glial secretions in health and disease could be utilized to reveal disease conditions and to determine the response to treatment. Upon activation, glial cells release a number of proteins, non-protein mediators or signaling molecules that beneficially or detrimentally affect neuronal functions and viability (Fig. 1). The neuroprotective or neurotoxic nature of glia is mainly determined by; degree of control of the glial environment, signals from injured neurons, and infiltrating immune/inflammatory cells [46].

It needs the development and application of innovative technologies that bridge the disciplines of chemistry and biology, thus accrediting the philosophy that biomedical problems often require creative multidisciplinary approaches. The applications of appropriate concepts of systems biology and omics technologies are crucial in this context. The proteomic approach has been used to analyze systematically the secreted proteins of astrocytes [32,47–51], microglia [52,53] and other glial cells like Schwann cells [54] and olfactory ensheathing cells (OECs) [55]. Microglia and astrocytes secrete numerous proteins that play important roles in the physiology and pathology of the CNS, and these proteins also interact with each other [56–60]. A prime example is provided by the chemokines, which are small, secreted proteins with important roles in cellular migration and intercellular communication. Furthermore, the chemokines having a cluster of functional roles in inflammatory conditions are prerequisite for the recruitment and activation of specific leukocyte subsets at sites of inflammation and for the development and homeostasis of lymphoid and nonlymphoid tissues. Recent reports have demonstrated that chemokines and their receptors are key signaling molecules in neuroinflammatory processes and in the development and functioning of the CNS. In fact, neurons and glial cells, including astrocytes, oligodendrocytes, and microglia, have been identified as cellular sources and/or targets of chemokines produced in the CNS under physiological and pathological conditions [61]. Glanzer et al. utilized a unique genomic and proteomic platform to determine the transcriptional, proteomic, and secretory profiles of seemingly neurotrophic microglial cells [62].

2.1. Microglial secretome

Microglia are resident immune cells in the CNS with phagocytic activity, and play crucial roles in the recognition, engulfment, and clearance of apoptotic cells and invading microbes. Proteins secreted by activated glia affect microglial phagocytic activity. Activated microglia manifest a variety of effector functions. In addition to phagocytosis and antigen presentation [63], they possess the ability to profoundly influence the initiation and progression of disease. Without a doubt, a greater understanding of microglia and their roles in brain disease will likely lead to novel means to control glial activation pathways, which in turn affect neuroprotective responses and secondary neurodegeneration. Microglia are well known for producing specialized responses in reaction to unique stimuli [64]. In response to a variety of insults, microglial cells release specific cocktails of inflammatory mediators, particularly high levels of proinflammatory cytokines and chemokines, which are often involved in CNS injury. As important elements of first line defense after the recognition of a stressor stimulus, activated microglia accumulate at sites of tissue

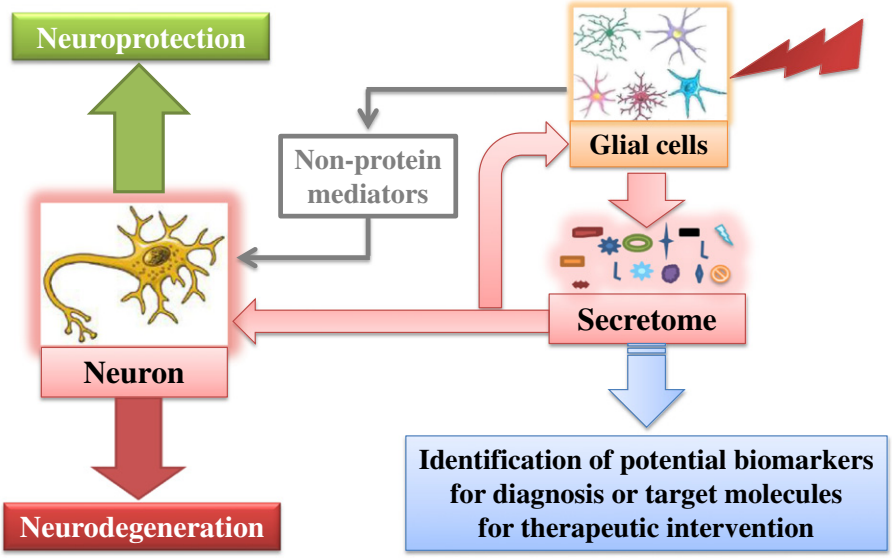

Fig. 1. Roles of the glial secretome in healthy and diseased CNS. Reactive glial cells secrete collection of proteins and non-protein mediators under inflammatory or pathological conditions, and some of these secreted proteins play a crucial role in the progression of inflammatory diseases of the nervous system. These secreted proteins could serve as diagnostic and prognostic biomarkers or for the treatment of brain disorders.