Chapter 1

Introductory Chapter: The Importance of Astrocytes in the Research of CNS Diseases

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Additional information is available at the end of the chapter

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1. Introduction

Glial cells were identified for the first time in the nineteenth century when the French physician René Dutrochet described for the first time, in 1824, small globules among the large ones within the mollusk nervous system. However, we have to wait until 1856 when the German pathologist Rudolph Virchow coined the term "nervekitt," nerve glue, to describe that sort of connective tissue of the central nervous system. Subsequently, Santiago Ramon y Cajal, Pio del Rio Hortega, and Otto Deiters pioneered this field with their experiments and gave them the name "glia" derived from the ancient Greek word that means glue. At that time, glia was considered as purely unfunctional glue for neurons [1]. However, research since the mid-1990 has shown that glia might play a particularly important role in the cognitive function as indicated by the correlation between the glia/neuron ratio in brain tissue and the state of evolution of species [2]. In fact, *C. elegans* possesses only 52 glial cells versus 302 neurons with a glia-to-neuron ratio of 0.18 [3], whereas the whole human-adult brain has a one-to-one ratio [4] and with a ratio of 1.4 in the cerebral cortex [5]. Moreover, comparison of glia-to-neuron ratio in different human cortical areas with that of macaques displayed a significant augmentation of the ratio in humans [6]. In the CNS, glia includes astrocytes, oligodendrocytes, microglia, and their progenitors NG2 glia and decades of studies demonstrated that they have a specific role in brain tissue homeostasis. In particular, astrocytes, whose name derived from Greek and means "star-like cell," are active dynamic signaling players of the central nervous system. They are key regulators of synaptic activity and plasticity, neural network, and cognitive functions controlling extracellular ion balance and neurotransmitter homeostasis. They perform many functions, including biochemical support of endothelial cells that form the blood-brain barrier, provision of nutrients to the nervous tissue, and regulation of neurogenesis and brain wiring [7]. Dysfunction of astrocytes can thereby induce major alterations

in neuronal functions, contributing to the pathogenesis of several brain disorders. Astrocytes participate to a variety of essential physiological processes in the healthy brain such as the formation and maturation of the synapses, receptor trafficking, control of the homeostasis of ions and energy metabolites, and clearance of neurotransmitters. Astrocytes also regulate the extracellular space volume and modulate the synaptic plasticity [8, 9]. Dynamic bidirectional signaling between neurons and astrocytes has been extensively demonstrated in experimental animal models. However, recently Navarrete et al. [10] demonstrated that astrocyte from human brain tissue exhibit Ca^{2+}-induced excitability and can respond to neurotransmitters released by synapses. Moreover, morphological, genomic, and functional studies revealed that human astrocytes display specific characteristics compared to the rodent counterparts. In particular, human astrocytes express more proteins involved in calcium signaling and propagate calcium waves at a higher speed compared to murine astrocytes [11]. These observations lead to the idea that human astrocytes play an important role in the molding of the higher cognitive functions and that they give a significant contribution to cerebral pathology. As a matter of fact, transplantation of human astrocytes into mouse brain leads to an improvement of higher cognitive functions, such as long-term potentiation (LTP) and learning, pointing toward the importance of human astrocytes in the cognitive abilities of human brains [2].

Indeed, even if several neuropathologists, such as Alzheimer, Nissl, and Fromman, speculate a glial role in neurodegenerative disorders, until the mid-1990s, the neurocentric paradigm dominated. Nevertheless, growing evidences indicate that astroglial dysfunction contributes to the pathogenesis of several neurological and psychiatric disorders [12]. A common feature of several neurological diseases is reactive astrogliosis.

2. Reactive astrogliosis

Reactive astrogliosis is a spectrum of changes in astrocytes that occur in response of all forms of CNS injury and disease. In summary, injured tissues display upregulation of structural proteins, such as glial fibrillary acidic protein (GFAP) and vimentin, and hypertrophy of astrocytes' cell body and processes that elongate around the lesion core and release a cascade of inflammatory signals that can strongly affect the pathological outcome [13]. Moreover, some quiescent astrocytes re-enter the cell cycle [14]. However, these hallmarks can vary according to the severity of the disease and are regulated by inter- and intracellular signaling molecules in a context-specific manner [15]. In particular, in mild or moderate astrogliosis, which generally occurs far from CNS focal lesions, astrocytic proliferation is almost absent and the increased GFAP expression together with cell body and process hypertrophy, which is not altering astrocyte organization into individual distinct domains, are variable [16]. Moreover, moderate astrogliosis also results in the expression of copper-zinc superoxide dismutase, glutathione peroxidase or metallothionein, inducible nitric oxide synthase, and release of trophic factors and cytokines, including tumor necrosis factor and interleukins and interferons [17]. Furthermore, in mild or moderate forms, if the initial triggering insult is removed, reactive astrogliosis can revert and cells return to a condition similar to that observed in healthy tissue [15]. On the other hand, near focal lesions, severe diffuse astrogliosis is characterized by significantly increased astrocytic

proliferation. The molecular factors that induce astrocytes' proliferation are not completely characterized, but several studies ascribe an important role to epidermal growth factor, fibroblast growth factor, endothelin 1, ATP, lipopolysaccharide, and nitric oxide [18–21]. Astrocytic proliferation causes overlapping of neighboring astrocytic processes with the disruption of the individual astrocyte domains and the consequent formation of a compact glial scar. Such scar, which represents the hallmark of reactive astrogliosis, is due to astrocyte interaction with different cell types of the brain tissue and is characterized by phenomena of necrosis, tumors, chronic neurodegeneration, infection, or inflammatory infiltration [15, 21]. These structural changes are not reversible and persist also after the resolution of the triggering insult [15]. More important, mature glial scars act as barriers to inflammatory cells to protect surrounding healthy tissue from nearby areas of intense inflammation. Reactive astrocytes can also protect CNS cells and tissue by up-taking excitotoxic glutamate, producing glutathione against oxidative stress, degrading amyloid-beta peptides, regulating extracellular space volume and ion balance, facilitating blood-brain barrier repair, and regulating CNS inflammation. Nevertheless, growing evidence also shows that reactive astrocytes can contribute to or be the primary source of CNS physiopathology. Reactive astrocytes from glial scars can indeed synthesize collagen and sulfate proteoglycans, which prevent axon regeneration [17].

3. Astrocytes: new tools for neurological disease research

Traditionally, astrocytes have been studied as a homogeneous group of cells, even if the peculiar morphology of mature mammalian astrocytes was observed since 1865 thanks to the studies on mouse brain by Otto Deiters [22]. A detailed morphological study of glial cells came from Camillo Golgi and Ramon y Cajal in 1872 who, independently, by means of the black staining reaction, observed two different types of astrocytes: the protoplasmic and the fibrous astrocytes. However, for a long time, astrocytes received little or no consideration as target for neurological studies because the neurocentric paradigm dominated. New and recent findings demonstrated that astrocytes are positioned to promote both the regeneration of the damaged neurons and to protect existing neurons from degeneration. For this reason, astrocytes represent an important focus in the development of new therapeutic tools for neurodegenerative disorder that have been historically viewed as purely neuronal in their pathology. Within the past 5 years, important progress has been made deriving astrocytes from induced pluripotent stem cells (IPSC). Researchers are now able to generate patients-specific astrocytes that recapitulate the patients' genetic background. Once healthy astrocytes have been obtained and characterized, they can be used to replace dying astrocytes or to promote the survival of existing neurons. This kind of application has not yet been tested in humans; however, there is a growing body of *in vitro* and *in vivo* evidence that indicates that these therapies would be beneficial for many neuronal diseases [23]. Indeed, in an amyotrophic lateral sclerosis (ALS) mouse model, researchers have shown that the direct transplantation of human (h)iPSC-derived neural progenitor cells prolonged the lifespan of the animal [24]. In these experiments, NPCs differentiated into astrocytes and exhibited an upregulation of vascular endothelial growth factor (VEGF), which induces the activation of the AKT-dependent intracellular signaling, which has previously been shown to be important for cell survival

and proliferation in ALS [25]. The authors also hypothesized that the introduction of progenitor-derived astrocytes with normal expression of glucose transporters could restore glucose homeostasis in this model [26]. Moreover, these versatile human astrocytes could be used alone or in co-culture with neurons in both target-based and phenotypic high-throughput drug-screening research studies, promoting the discovery of novel therapeutics tools useful in the treatment of neurodegenerative disorders. For decades, therapeutic development for neurodegenerative disorders has focused only on diseased neurons. Due to the crucial role of astrocytes in physiology of the central nervous system and in the pathogenesis of several neurodegenerative diseases, it is not surprising that the traditional drug development strategy which follows the neurocentric paradigm has not produced effective therapies. Developing new drugs that complement and combine therapies which target both neuronal and astrocytic degeneration could provide a new direction to increase the success of therapeutic development for neurodegenerative diseases in the future. The shift from a neurocentric view to one that incorporates astrocytes in disease models for drug discovery is a critical step in renewing drug development strategies to treat neurodegenerative diseases.

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