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Review

Glial cells in amyotrophic lateral sclerosis

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ABSTRACT

For more than twenty years glial cells have been implicated in the pathogenetic cascades for genetic and sporadic forms of ALS. The biological role of glia, including the principal CNS glia, astroglia and oligodendroglia, as well as the myeloid derived microglia, has uniformly led to converging data sets that implicate these diverse cells in the degeneration of neurons in ALS. Originating as studies in postmortem human brain implicating astroglia, the research progressed to strongly implicate microglia and contributors to CNS injury in all forms of ALS. Most recently and unexpectedly, oligodendroglia have also been shown in animal model systems and human brain to play an early role in the dysfunction and death of ALS neurons. These studies have identified a number of diverse cellular cascades that could be, or have already been, the target of therapeutic interventions. Understanding the temporal and regional role of these cells and the magnitude of their contribution will be important for future interventions. Employing markers of these cell types may also allow for future important patient subgrouping and pharmacodynamic drug development tools.

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Introduction

Amyotrophic lateral sclerosis is a motor neuron disease affecting the upper and lower motor neurons in the motor cortex, brain stem and spinal cord. Currently, there is no effective cure available to halt or delay disease from progressing. Over the past 20 years multiple genes that cause disease have been identified, most notably mutations in the Super Oxide Dismutase 1 (SOD1) gene and repeat expansions in the first intron of the C9ORF72 gene. Moreover, pathology associated with a very rare genetic form of ALS, TDP-43, is thought to be involved in disease pathogenesis in the majority of ALS patients (Neumann et al., 2006). The discovery of different disease causing mutations has led to the development of ALS animal models, which provide researchers a tool to better understand disease mechanisms. For the past 20 years, the mSOD1 transgenic

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overexpression mouse and rat model has been the most widely studied animal model to study disease mechanisms and therapeutics (Gurney et al., 1994). More recently, some TDP-43 animal models have been generated, but their true potential for studying disease pathogenesis and drug discovery remains uncertain.

Studies using ALS animal models have taught us that the well-being of neurons in general, specifically motor neurons, is highly dependent on a whole range of other cell types, commonly named glial cells, which surround motor neurons and provide nutritional and trophic support to them. The study of glial cells in the past has led to the conclusion that ALS is a non-cell autonomous multifactorial disease in which many cell types as well as divergent disease mechanisms all converge to the focal death of interneurons and motor neurons. This review will introduce the different glial cell types in the CNS and provide an overview of the role of glial cells in motor neuron degeneration. Several potential relevant disease mechanisms for each specific glial subtype will be mentioned. These have led to the development of therapeutics specifically targeting the glial compartment.

Glial cellular reaction in ALS

Microglia and immune reactivity

Microglial cells are of mesodermal origin and the main immune-competent cells of the central nervous system. Microglia release a whole range of pro-inflammatory versus anti-inflammatory cytokines and chemokines when encountering any damaging hazard. They will respond through the release of pro-inflammatory (so-called 'classically activated' or M1, with release of e.g., tumor necrosis factor alpha (TNFα), interferon 1beta (IL-1β), nitric oxide (NO), O_2, and interferon gamma (IFN-γ)) factors which clear and/or limit biological hazards followed by the release of anti-inflammatory (so-called 'alternatively activated' M2, with release of e.g., interleukin 4 (IL-4), IL-10, and insulin growth factor 1 (IGF-1)) factors which repair and mediate restoration. Microglial cells function in close interaction with inflammatory T-cells as well as with astrocytes in mediating this inflammatory response. Microglia do not exclusively express either M1 or M2 cytokines and can release different combinations of cytokines and chemokines depending on the environment they are exposed to and their direct interaction with other cells, and so may present a different phenotype at different time points and locations in the CNS.

In ALS patients as well as in ALS rodent models, there is a clear microglial reaction characterized by the upregulation of a whole range of markers used to identify microglia like CD11b and Iba1 as well as an upregulation of markers associated with antigen presentation like CD11c, intracellular adhesion molecule 1 (ICAM-1) and CD86, suggesting that microglial cells closely interact with concomitant infiltrates of inflammatory T-cells (Alexianu et al., 2001; Corcia et al., 2012; Henkel et al., 2004, 2006; Turner et al., 2004). Similarly, microglia increase in the release of pro-inflammatory cytokines as well as chemokines (Henkel et al., 2004, 2006; Hensley et al., 2003; Meissner et al., 2010; Nguyen et al., 2001; Poloni et al., 2000). Analysis of microgliosis in ALS patient CNS largely depends on studies of postmortem tissue, which demonstrate increased microgliosis in the motor cortex, the motor nuclei of the brain stem, the corticospinal tract and the ventral horn of the spinal cord (Kawamata et al., 1992). Live in vivo PET scanning with ^{11}C-PK11195, a ligand that highly binds to CNS microglia, as well as other CNS cells to a lesser extent, reveals apparent microgliosis in ALS patients, suggesting a correlation between the extent of microgliosis and damage to upper motor neurons, but not lower motor neurons (Turner et al., 2004). Another microglial imaging approach uses a radioligand of the translocator protein (TSPO), upregulated by microglia upon microglial activation (Corcia et al., 2012). Significant microgliosis was detected in the primary motor cortex, supplementary motor cortex and temporal cortex (Corcia et al., 2012).

In mSOD1 animal models, there is an increase in microglial reactivity in the ventral horn of the spinal cord, which follows closely the nerve de-innervation at the neuromuscular junction, one of the first pathological signs of motor neuron degeneration (Alexianu et al., 2001; Saxena et al., 2009). This microglial reaction in the CNS is thought to be mainly mediated by local proliferation, rather than infiltration and microglial differentiation of myeloid cells from the blood stream through the blood–brain barrier (BBB) (Ajami et al., 2007; Gowing et al., 2008).

Interestingly other myeloid (cells from myeloid origin like monocytes, macrophages and microglia) subtypes might contribute to the overall 'microglial' reaction and motor neuron degeneration. A recent study indicated that Ly6C+ spleen derived monocytes are recruited to the spinal cord of mSOD1 mice by CCL2 expressing resident microglia (Butovsky et al., 2012). Concomitantly with this infiltration of Ly6C+ monocytes, CD39+ resident microglial cells are degenerating, suggesting against a so-called 'microgliosis' but rather a decrease in resident microglia and increase in spleen derived monocytes. These Ly6C+ macrophages in mSOD1 mice seem to accelerate the loss of motor neurons as anti-Ly6C antibody treatment lead to a significant prolongation of life span in mSOD1 mice. Interestingly, similar to what is seen in the mSOD1 mice, M1-primed monocytes accumulate in the spinal cord of ALS patients. It has not been proven however if the resident microglia were truly dying in contrast to losing immunoreactivity for the marker used to identify these cells. In addition, technical limitations in identifying the origin of specific myeloid subsets prevail, as irradiation and transplantation of bone marrow cells cause non-physiological damage to the BBB and a non-physiological influx of progenitor cells and might impair the conclusions drawn from this study (Ajami et al., 2007). Another recent study performing transcriptional profiling of microglial cells in the spinal cord of mSOD1 mice failed to confirm the presence of Ly6C expressing infiltrating macrophages in the spinal cord (Chiu et al., 2013). The authors suggested that resident microglial cells increased in the spinal cord of mSOD1 mice whereas monocytes did not (Chiu et al., 2013). Given the discrepancies of this study as compared to others, it remains to be fully elucidated whether infiltrating monocytes truly contribute to motor neuron disease. Importantly the translation of the numerous transgenic mouse studies has not been equally carried out in human ALS tissue — making difficult comprehensive assumptions regarding relevance to human disease.

Astroglia

Astrocytes are ectodermal cells involved in ion homeostasis, neurotransmitter recycling and metabolic support to surrounding neurons. One of the most important and extensively studied supportive functions of astrocytes is their involvement in the glutamate–glutamine cycle (Danbolt, 2001). Glutamate is one of the most important neurotransmitters in the CNS mediating excitatory synaptic communication between neurons. Uptake of glutamate from the synaptic cleft between presynaptic and postsynaptic neurons through glutamate transporters EAAT2 (GLT-1 in rodents) and EAAT1 (GLAST in rodents) expressed by astrocytes will prevent excessive postsynaptic stimulation of glutamate receptors and motor neuron cell death, a process which is called glutamate mediated excitotoxicity. Another important function for astrocytes is their involvement in the metabolic support of neurons. Astrocytes are tightly coupled to the bloodstream and strongly interconnected through gap-junctions through which they provide metabolic substrates over long distances. Under conditions of increased neuronal activity and metabolic substrate demand, astrocytes increase their glycolytic activity, converting glucose to lactate (Pellerin and Magistretti, 1994). Both glucose and lactate are hypothesized to be distributed by astrocytes and gap-junction connected oligodendrocytes throughout the parenchyma and used as an energy substrate by neurons (Funfschilling et al., 2012; Lee et al., 2012). Like microglia, the astrocyte function is highly influenced by T-cells, (motor)-neurons and possibly oligodendrocytes. Astrocytes are usually identified by