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Mini-review

Role of GFAP in CNS injuries

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HIGHLIGHTS

- The response to CNS injury is altered in multiple ways in GFAP null mice.
- There is considerable variability in findings of the effects of the GFAP null.
- GFAP function likely differs depending on CNS region and other variables.

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ABSTRACT

The role of GFAP in CNS injury is reviewed as revealed by studies using GFAP null mice. In order to provide background information for these studies, the effects of absence of GFAP in the uninjured astrocyte are also described. Activities attributable to GFAP include suppressing neuronal proliferation and neurite extension in the mature brain, forming a physical barrier to isolate damaged tissue, regulating blood flow following ischemia, contributing to the blood–brain barrier, supporting myelination, and providing mechanical strength. However, findings for many of these roles have been variable among laboratories, pointing to the presence of unappreciated complexity in GFAP function. One complexity may be regional differences in GFAP activities; others are yet to be discovered.

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1. Introduction

Glial fibrillary acidic protein (GFAP) is an intermediate filament protein that is primarily expressed in astrocytes (reviewed in [1]). The evolution of a specific intermediate filament protein for astrocytes suggests that the protein plays a critical role, and its marked upregulation in CNS injury indicates that one of these is in injury damage control. This review exams the role of GFAP in CNS injuries; and to provide a foundation for this topic, also describes what is known about GFAP function in the uninjured state. Studies covered are largely limited to those investigating effects solely attributable to GFAP, and thus a substantial body of work examining the consequences of absence of both GFAP and vimentin [2] is not discussed, except when it enlightens findings obtained for GFAP alone. A subtheme for this review arises from the remarkably discrepant results among laboratories for findings of GFAP functions. There has been a tendency for each laboratory to question (albeit tacitly) the competence of their competitors who present contrary observations, but the more likely explanation, and the one adopted here, is that these differences advertise complexities not yet appreciated, and provide an opportunity for deeper understanding of the astrocyte repertoire.

2. GFAP overexpression

One approach to investigate the role of GFAP is to increase its expression as occurs during the reactive response to determine what other changes might occur, whereas another is to prevent GFAP upregulation, or to knock it out altogether. The former approach was undertaken by Messing et al. [3], who used a human GFAP transgene to increase GFAP expression in astrocytes, thus avoiding the confounding effects of an actual injury. Unexpectedly, chronically high GFAP levels proved lethal, and were accompanied by abundant deposition of GFAP-containing protein aggregates in astrocytes. These observations led to GFAP mutations being identified as the major cause of Alexander disease, a usually fatal neurodegenerative disorder characterized by astrocytic inclusions (reviewed in [4]). However, as the mutations appear to act by a gain of toxic function mechanism [4], this approach of chronic overexpression of GFAP does not provide information about the normal role of the protein in injury.

3. GFAP null mice

Suppression of GFAP expression was first accomplished by transfecting U251 astrocytoma cells with a GFAP antisense construct [5]. Whereas control U251 cells robustly extended processes when co-cultured with neurons, this response was almost completely absent in the transfected cells. Given the importance of astrocytic processes for guiding neuronal migration, inducing the blood–brain barrier, and ensheathing synapses, this requirement for GFAP for process extension suggested that a GFAP null mouse would be a dead mouse. Undeterred, four laboratories independently produced GFAP knockouts within a year of each other, and found them viable. Three of these groups, Gomi et al. [6], Pekny et al. [7] and McCall et al. [8], reported very similar findings of minimal effects of GFAP absence. All found normal development, growth, fertility and lifespan. All three also reported no difference from wild type in brain architecture, including unchanged numbers of neurons and astrocytes. No compensatory increase in any other intermediate filament was observed. The blood–brain barrier was found intact as judged by electron microscopy and exclusion of Evans blue and microperoxidase, the latter having a molecular weight of just 1862. Overt behavior and motor activity were normal.

The GFAP null line produced by the fourth group, Liedtke et al. [9], was also viable, but displayed some striking defects. Half the null mice older than 18 months developed hydrocephalus. Null mice over 18 months of age also had decreased levels of corpus callosum myelin, and 6 month old null mice had less myelination of the anterior column of the spinal cord, some non-myelinated axons in both the spinal cord and optic nerve, and myelinating, hyperplastic oligodendrocytes in the optic nerve. Significantly fewer total blood vessels, especially of larger diameter, were found in the white matter of optic nerve and spinal cord at 4 months of age. Despite the aberrant morphology involving the optic nerve, there was no difference in its thickness, and visual evoked potentials in the visual cortex were normal. Use of ^{125}I-albumin revealed leakage of the blood–brain barrier in the lumbar spinal cord of mice over 1 year of age. These differences in tissue architecture in the spinal cord and optic nerve were apparently region specific, as no differences were seen in the cerebrum, brainstem, or cerebellum; although subsequently, Gimenez et al. [10] did report the presence of some disruption of myelin sheaths in the cerebellar white matter and granular layer of the Pekny et al. [7] GFAP null mouse. The other three laboratories may have missed observing the hydrocephalus because their mice were not followed beyond 14 months of age, but they also did not observe the changes in myelination, vascularization and blood–brain barrier that occurred much earlier in the Liedtke line. These analyses included ultrastructural study of the spinal cord, which found the diameter of blood vessels to be larger, rather than smaller than wild type [7,11], and of the optic nerve [8]. Thus the differences between the Liedtke line and those of the other groups arise from some unknown conditions interacting with the GFAP null. The basis for these different observations has not been pursued; doing so could provide a wealth of information about interacting partners of GFAP that regulate its roles in CNS development and function.

4. Astrocyte processes

The state of astrocytic processes in the GFAP nulls is of particular interest given the prior finding in cell culture of their dramatic reduction in the absence of GFAP [5]. When these experiments were repeated using GFAP null primary astrocytes in place of transfected U251 cells, the results were not replicated [12]; instead, process extension by the cultured GFAP null astrocytes in response to neurons was indistinguishable from wild type. A subsequent analysis of GFAP null astrocytes cultured alone also showed no difference in morphology from wild type astrocytes [13]. In vivo, observations at the light microscope level of astrocytic processes in GFAP null mice found them to extend normally to and around blood vessels in the hippocampus [6], and ultrastructural examination of the hippocampus also found no differences from wild type [7,8]. However, in the optic nerve astrocytic processes were observed to be smaller than in the wild type [8], including those extending to the pial surface or to blood vessels. In the spinal cord, an ultrastructural study of the lateral funiculus [7] observed no difference in astrocyte process size, but an ultrastructural analysis in the anterior column of the cervical spinal cord at C7 revealed astrocyte processes to be short and club-like, and extracellular space increased [9]. Findings for the cerebellum of GFAP null mice mirror those of the spinal cord in inconsistency. Shibuki et al. [14] observed no differences in the structure of the cerebellum between GFAP null and wild type mice using detailed light and electron microscopic studies, but ultrastructural analysis by Gimenez et al. [10] found Bergmann glial processes were shorter and thinner, and more extracellular space was present. Glial coverage was incomplete of Purkinje cell soma, Purkinje dendrites, the vasculature, and the pial surface, and the endfeet did