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Origin, lineage and function of cerebellar glia

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ABSTRACT

The glial cells of the cerebellum, and particularly astrocytes and oligodendrocytes, are characterized by a remarkable phenotypic variety, in which highly peculiar morphological features are associated with specific functional features, unique among the glial cells of the entire CNS. Here, we provide a critical report about the present knowledge of the development of cerebellar glia, including lineage relationships between cerebellar neurons, astrocytes and oligodendrocytes, the origins and the genesis of the repertoire of glial types, and the processes underlying their acquisition of mature morphological and functional traits. In parallel, we describe and discuss some fundamental roles played by specific categories of glial cells during cerebellar development. In particular, we propose that Bergmann glia exerts a crucial scaffolding activity that, together with the organizing function of Purkinje cells, is necessary to achieve the normal pattern of foliation and layering of the cerebellar cortex. Moreover, we discuss some of the functional tasks of cerebellar astrocytes and oligodendrocytes that are distinctive of cerebellar glia throughout the CNS. Notably, we report about the regulation of synaptic signalling in the molecular and granular layer mediated by Bergmann glia and parenchymal astrocytes, and the functional interaction between oligodendrocyte precursor cells and neurons. On the whole, this review provides an extensive overview of the available literature and some novel insights about the origin and differentiation of the variety of cerebellar glial cells and their function in the developing and mature cerebellum.

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Abbreviations: AMPA, a-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BG, Bergmann glia; EGL, external granular layer; FGF, fibroblast growth factor; GLAST, glutamate/aspartate transporter; MN, midkine; NRG, neuregulin; PTN, pleiotropin; PTPζ, protein tyrosine phosphatase zeta; OPC, oligodendrocyte precursor cell; PWM, prospective white matter; RL, rhombic lip; VN, ventricular neuroetiphelium.

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1. Introduction

The anatomical and functional complexity of the cerebellum is reflected not only by the variety of its neuronal phenotypes, but also by a remarkable heterogeneity of astroglial and oligodendroglial cells. Many of these of glial types are also characterized by highly distinctive morphological features and functional properties, which are unique among the glial cells of the entire CNS. Cerebellar astrocytes and oligodendrocytes participate to crucial developmental processes and contribute to regulate physiological function in the mature cerebellum. However, while studies on cerebellar neurons and circuits have progressed during the last decades, less attention has been devoted to investigations on development, lineage, heterogeneity and functions of cerebellar glia. A comprehensive overview covering the actual knowledge on this topic, as well as the most critical issues that await clarification, is missing. Filling this gap is most important in view of the increasing relevance of glia in developmental processes and also to achieve a deeper understanding of the complexity of cerebellar structure and functioning. Here, we provide a critical review of the available data and present some personal views on the development of cerebellar astrocytes and oligodendrocytes. In addition, in order to support the concept that the peculiar features of cerebellar glia are required to carry out particular functional tasks, we discuss about the cerebellar-specific roles played by astrocytes and oligodendrocytes during development and in the operation of mature circuitries.

2. Origins and differentiation of cerebellar astrocytes

2.1. The phenotypic repertoire of cerebellar astrocytes

The glia of the cerebellum was first described and classified by Ramón y Cajal (1911) in three main categories, distinguished by their morphology and position in the cerebellar tissue: (i) the glial cells of the white matter (also including oligodendrocytes), characterized by processes oriented along the direction of axonal tracts, (ii) the astrocytes of the granular layer, with star-shaped bushy processes, and (iii) the "neuroepithelial cells with Bergmann fibres", featuring cell bodies aligned to Purkinje cell somata and several ascending processes spanning radially the molecular layer, up to their endfeet in contact with the subpial basement membrane. The latter cells were later called "Golgi epithelial cells" (Palay and Chan-Palay, 1974), but they are commonly known as Bergmann glia (BG), and here we shall use this term. This classification of cerebellar astrocytes was essentially confirmed by more recent essays (e.g. Palay and Chan-Palay, 1974; Altman and Bayer, 1997). Nonetheless, by the analysis of Golgi preparations with high-voltage electron microscopy, Chan-Palay and Palay (1972) discovered the veil-like appendages emanating from processes of granular layer astrocytes and BG and described their relationship with the local neuropil, suggesting a role in the compartmentation of the cortical circuitries. Accordingly, the Palays distinguished "velate" astrocytes, including the bushy cells of the granular layer and BG; "protoplasmic" astrocytes, a less represented type with slender processes devoid of lamellar appendages that is encountered in the cortex; and "fibrous" astrocytes, typical of the white matter (Palay and Chan-Palay, 1974). In spite of the morphological variety of the astrocytes that populate the different subdivisions of the mature cerebellum, in the following sections devoted to the ontogenesis of cerebellar astroglia we will exclusively refer to BG and parenchymal astrocytes (the latter comprising all the other categories).

2.2. Origin of cerebellar astrocytes from the ventricular neuroepithelium

Ramón y Cajal (1911) described the origin of cerebellar astrocytes through the comparative investigation of cerebellar development in different species. He concluded that all cerebellar glia derive from the ventricular neuroepithelium (VN) and proposed that BG results from the retraction of ependymal processes of radial glia of the cerebellar primordium. By the analysis of ^{3}H-thymidine-labelled material, Altman and Bayer (1997) defined the time course of generation of cerebellar glia from the VN of the embryonic cerebellar primordium. These authors assumed that after the completion of Purkinje cell genesis, at E16 in the rat, this germinal layer exclusively gives rise to non-neuronal elements. Therefore, at subsequent developmental stages (from E17 to birth) they identified two main sites of cell proliferation within the VN: a posterior one, located in front of the rhombic lip (RL), and a more anterior one, close to the isthmus and the nascent superior cerebellar peduncle. Altman and Bayer (1997) also noted that the cells that delaminate from the VN continue to divide in the overlying tissue and, hence, first proposed that cerebellar glia may be also generated by progenitors that proliferate within the cerebellar parenchyma. While it is now known that GABAergic interneurons also derive from parenchymal progenitors (Zhang and Goldman, 1996a; Maricich and Herrup, 1999; Leto et al., 2006), anatomical investigations of neurochemically identified glia (Yuasa, 1996; Yamada and Watanabe, 2002) and fate mapping analyses using inducible reporter genes expressed in radial glia essentially confirmed the VN origin of cerebellar astrocytes (Mori et al., 2006; Sudarov et al., 2011).

2.3. Origin of cerebellar astrocytes from the rhombic lip and the external granular layer?

While the VN generates GABAergic neurons and glia, other types of cerebellar neurons, and notably all glutamatergic neurons,