Chapter 27
Glial Cells

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Abstract The term "glia" describes the non-neuronal, electrically passive cells of the central nervous system, which were first defined as a distinct cell type by Rudolph Virchow in 1856, and derive their name from the Greek for "glue" due to their presumed primary function as connective tissue. The term is misleading however, as it implies a single cell type when it in fact encompasses three cell classes: oligodendrocytes, astrocytes, and microglia. The origins and roles of these different glial classes are quite distinct, but they have collectively been viewed as supportive cells that maintain a healthy microenvironment favourable to neuronal function, and play structural and protective roles throughout development. This traditional conception is now giving way to an appreciation that glial cells play an active and dynamic role in neurophysiology, in addition to providing passive support. This chapter outlines the origins, anatomy and primary roles of the major glial cells in the cerebellum.

Keywords Astrocyte • Oligodendrocyte • Microglia • Gliotransmission • Homeostasis

27.1 Gliogenesis and Glial Lineages

Gliogenesis is the developmental process by which all glial cell types are generated; both the production of glial progenitor cells and their differentiation into mature glia. There are two routes via which cerebellar glia develop, with macroglia (astrocytes and oligodendrocytes) deriving from the neuroepithelium (along with neurons), and microglia originating from the mesodermal haematopoietic lineage.

Neuroepithelial cells, which are embryonic stem cells capable of both neuronal and glial fates, undergo morphological and epigenetic modification such that by mid-gestation they have differentiated to become radial glial cells. It is from these

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progenitor cells that astrocytes and oligodendrocytes arise (Rowitch and Kriegstein 2010). Radial glia undergo either direct differentiation into astrocytes, or form oligodendrocyte precursor cells which are subsequently capable of further specialization into oligodendrocytes.

Microglia enter the cerebellum early in embryogenesis as circulating foetal macrophages, and are thought to 'seed' the developing brain (Ginhoux et al. 2013). Further transformation results in embryonic microglia that mature in early post-natal life.

27.2 Oligodendrocytes and Microglia

Oligodendrocytes are the myelinating cells of the central nervous system. In the cerebellar cortex, they myelinate the mossy and climbing fibre inputs, and the Purkinje neuron axons that are the sole output of the cerebellar cortex. Accordingly, oligodendrocytes are most commonly located in the lower granular layer and the white matter (Fig. 27.1). In the rat cerebellum, approximately seven axons are myelinated by each mature oligodendrocyte (Bakiri et al. 2011).

In addition to the classic myelinating oligodendrocytes, another class of non-myelinating cells also originate from oligodendrocyte precursors, but do not lose

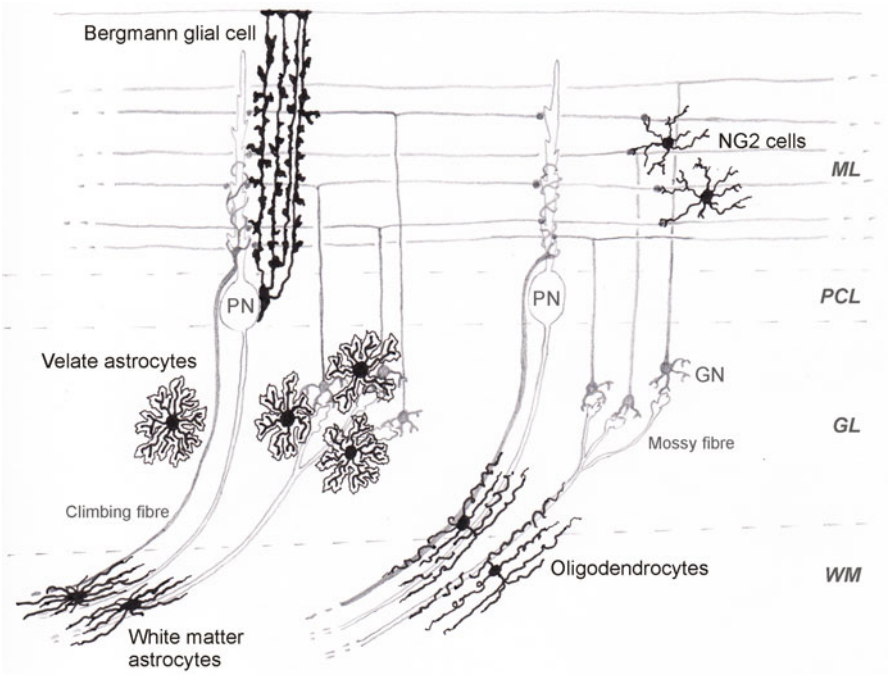

Fig. 27.1 Diagram of the cerebellar cortical layers with the most abundant macroglial cells present in each layer illustrated in *black*. *PN* Purkinje neuron, *GN* granule neuron, *ML* molecular layer, *PCL* Purkinje cell layer, *GL* granular layer, *WM* white matter

expression of the proteoglycan NG2 during differentiation. These cells are therefore referred to as NG2 cells (or polydendrocytes) and could potentially represent a fourth major class of central nervous system glial cell (Nishiyama et al. 2009). NG2 cells are found throughout the cortex, and have been shown to receive synaptic input from parallel and climbing fibres (Fig. 27.1). Their role and function is currently a matter of active debate.

The microglia of the cerebellum function in much the same way as elsewhere in the central nervous system. Under physiological conditions, microglia exist in a resting state, with each cell body possessing several fine ramified processes that encompass an individual domain or territory. Under pathophysiological conditions, such as following injury or disease, the cell retracts these processes and enters an activated state. Activated microglia are highly mobile, such that they are able to rapidly translocate to the site of injury and, if required, perform phagocytic duties. In addition to their immune response function, microglia also play a critical role during development by engulfing and eliminating synapses to refine network connectivity in the maturing brain (Paolicelli et al. 2011).

27.3 Astrocytes

Astrocytes are a heterogeneous population of cerebellar glia, comprising fibrous astrocytes of the white matter tracts and protoplasmic astrocytes of the grey matter (Fig. 27.1). In addition to anatomical location, these two classes of astroglia are also distinguished on a morphological basis – protoplasmic astrocytes have more heavily branched processes than fibrous astrocytes. The astrocyte population of the cerebellum functions as an interconnected network known as a syncytium, with individual cells connected via gap junctions that allow the controlled diffusion of small molecules between neighbouring cells.

Fibrous astrocyte somata within regions of white matter are arranged in rows between axonal bundles, with their processes forming perivascular endfeet and perinodal contacts. The protoplasmic astrocytes found in the granular layer are termed "velate" astrocytes, due to the sheet-like projections that spread through the neuropil, enclosing the mossy fibre glomeruli and so limiting diffusion of transmitter away from sites of release. The velate astrocytes are therefore thought to demarcate glomeruli and associated granule neurons into anatomical compartments, with the hypothesized function of segregating specific mossy fibre inputs (Hoogland and Kuhn 2010).

27.4 Bergmann Glia

In the molecular layer, the predominant astroglial cell is a type unique to the cerebellum: the Bergmann glial cell. Bergmann glia (sometimes termed Golgi epithelial cells) are classed as protoplasmic astrocytes, but retain much in common with the radial glia from which they are derived (Fig. 27.1).

Bergmann glial somata align with Purkinje neuron somata between the granular and molecular layers, and extend two or more long radial processes through the molecular layer to the pial surface, where they terminate in bulbous endfeet. After maturation, each of these primary Bergmann fibres becomes decorated with multiple elaborate membrane protrusions known as microdomains, which sprout from the fibre and project into the neuropil of the molecular layer as complex leaf-like structures with high surface area to volume ratios. These processes enclose all of the synapses within the molecular layer, both excitatory and inhibitory, thus restricting diffusion of neurotransmitter away from active synapses. In the rat cerebellum there are approximately eight Bergmann glia to every Purkinje neuron, with each glial cell providing coverage of up to 6000 synapses.

27.5 Astroglial Functions in the Cerebellum

Cerebellar astroglia carry out the same core roles as astrocytes elsewhere in the central nervous system. Many of these roles are supportive, and only key roles are covered here for brevity; see Kettenmann and Ransom (2012) for more details.

K^+ buffering is a major homeostatic mechanism by which increased extracellular K^+ released during action potential propagation is rapidly taken up by astrocytes (by virtue of their characteristically high K^+ membrane permeability at rest), and redistributed through the astrocyte syncytium to sites of lower concentration. Another key role is the recycling of neurotransmitters: astroglia express transporters for both glutamate and GABA positioned near sites of release that rapidly clear the transmitters from the extrasynaptic space. Within the cytosol, the transmitters are metabolized to glutamine, which is released back into the extracellular space for reuptake by neurons. Finally, astrocytes can undergo a phenotypic change in response to noxious stimuli, adopting a quasi-immune cell state; a process known as reactive gliosis. This "activation" of astrocytes accompanies neuropathology, and can be both beneficial and detrimental to resolution of the injury or infection.

In addition to these general functions of astrocytes, Bergmann glia also play a crucial role in directing neuronal migration during development. Granule neuron precursor cells in the immature cerebellum are initially positioned as an external layer, but migrate along the radial Bergmann glial fibres (at that stage, lacking microdomain protrusions), to reach the internal granular layer in the adult cerebellum.

Finally, a major development in our understanding of astroglia that has emerged over the last few decades is the realization that these cells also play an active role in modulating neuronal function. In addition to expression of neurotransmitter transporters, astroglial processes also express both ionotropic and metabotropic receptors. These receptors are commonly linked to calcium signalling pathways, and so enable the astrocytes to detect and respond to synaptic transmission.

Calcium elevation can lead to release of neuromodulators from astrocytes that feed back to the neuronal network, modifying activity – a process termed

"gliotransmission" – which has been implicated in a wide range of neuronal processes, including synaptogenesis, neurovascular coupling, synchronization of network activity, and synaptic plasticity (Haydon 2001). In Bergmann glia, disruption of glutamate-evoked calcium signalling causes dysregulation of synaptic transmission to Purkinje neurons and motor defects, confirming the active role that neuron-glial signalling has in establishing proper connectivity and regulation of the cortical microcircuit. It is becoming increasingly clear that such bi-directional communication between neurons and glia is essential for proper cerebellar function, throughout development.

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