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Dynamic structural remodelling of microglia in health and disease: A review of the models, the signals and the mechanisms

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ABSTRACT

Microglia are unique cells within the central nervous system because of their biophysical independence. As a result of this unusual property the cells must undergo significant structural remodelling in order to engage and connect with other elements within the central nervous system. Efficient remodelling is required for all activities that microglia are involved in ranging from monitoring synaptic information flow through to phagocytosis of tissue debris. Despite the fact that morphological remodelling is a prerequisite to all microglial activities, relatively little research has been undertaken on the topic. This review examines what is known about how microglia transform themselves during development, under physiological conditions in response to changes in neuronal activity, and under pathological circumstances. Specific attention is given to exploring a variety of models that have been proposed to account for microglial transformation as well as the signals that are known to trigger these transformations.

1. Introduction

Microglia have long been recognised to possess macrophage-like abilities within the central nervous system (CNS). These cells have been extensively implicated in responding to tissue damage and destruction, producing a vast array of inflammatory mediators to coordinate the actions and activities of other cells involved in the repair response. Accordingly, microglia have been identified to play a critical role in contributing to neurodegenerative diseases such as Alzheimer's and Parkinson's disease. More recently, it has also become apparent that microglia are as important in regulating the activity of the CNS in the absence of disease. Specifically, a number of studies have now demonstrated that microglia play an integral role in responding to neuronal activity and in regulating synaptic connectivity.

Quite unlike neurons, astrocytes, NG2 cells, and oligodendrocytes, microglia are not permanently connected physically or electrically to neighbouring cells. Graeber (2010) has recently suggested that being 'outsiders' within the CNS places microglia in a unique position to monitor and respond to unusual fluctuations in their immediate microenvironment. The relative independence of microglia gives rise to a further unusual property, which is their ability to engage in profound morphological transformation. When microglia identify changes in their environment they typically reorganise their structure to directly send some or all of their cellular processes to a site of interest, or in more extreme circumstances entirely relocate their cell body. So well-recognised is the ability of microglia to undergo structural transformation that it has become used as a surrogate index of microglial activation. For the most part, attention within the literature has been focused upon what microglia do once they arrive at a site of action; however the process of traversing the CNS is not straightforward. Microglia are embedded in an incredibly dense milieu of vasculature, extracellular matrix (ECM), and a raft of other densely interconnected cells. Remodelling and traversing within this environment is a non-trivial activity. Against this background, the principal objective of the current review is to examine the literature that has investigated how microglia transform themselves in order to interact and engage with other elements within the CNS.

2. Microglial morphology: first observations to first quantification

While the existence of neuro-glial cells had been accepted as fact by the mid nineteenth century it was not until the early twentieth century that microglia were recognized to represent a

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distinct cell type within the CNS. Arguably, the single most critical development leading to this realization was the application of histochemical-based stains that clearly differentiated the unique morphology of microglia. Robertson (1899) was the first to identify that a platinum stain was not taken up by neurons or astrocytes but was absorbed by a third cell type, which were characterized by small somas with multiple processes emanating in all directions. The work of Robertson was later elaborated by Rio-Hortega (1917), who was the first to explicitly use the term microglia. Using silver carbonate staining, Rio-Hortega described the existence of cells possessing numerous primary processes that branched extensively, each terminating with fine tapered tips. He observed that these cells were not stationary and were capable of consuming cellular debris. Following these seminal contributions, Dougherty (1944) made the additional observation that microglial morphology differed substantially with respect to the cells' location within the CNS. Specifically, he identified that microglia were frequently found directly opposed to cerebral vasculature, wrapping their processes around vessels, and often extending processes longitudinally along their length (Rezaie and Male, 2002).

Following the early descriptive studies of Robertson (1899), Rio-Hortega (1917) and Dougherty (1944) the next major development in understanding the morphological characteristics of microglia in the healthy brain came from Lawson et al. (1990). This study identified that the morphology of microglia varied much more substantially than had previously been reported with cells ranging from small and sparse in the cerebellum to relatively tightly packed in cortical regions. Despite the clear heterogeneity of form, Lawson et al. (1990) suggested that microglia could be categorized into three broadly distinct subtypes: compact, longitudinally branched, and radially branched (see Fig. 1). Compact cells were observed to have small, simple soma with short, unbranched processes (Fig. 1A). Longitudinally and radially branched cells were characterized as having three to five processes emanating from round or elongated cell bodies, with a high degree of secondary and tertiary branching. While longitudinally branched microglia were almost always found in white matter tracts, with processes running parallel to the axonal fibers (Fig. 1B), radially branched microglia were more exclusive to grey matter (Fig. 1C). These observations were similar to those reported by Dougherty (1944) years prior, but Lawson et al. (1990) quantified important parameters reflecting the size and "branchiness" of microglia using manual traces of microglia. Measures of the cells' area, perimeter, and convex hull area indicated that the cells' local environment was likely to be a significant determinant of microglial morphology, as factors such as microglial cell density and general neuronal viability did not correlate well with microglial phenotype.

In a study complementary to Lawson et al. (1990), Vela et al. (1995) described that microglial morphology also varied substantially across the different subregions of the cerebellum, particularly with respect to size and density. The molecular layer displayed the least dense microglial population, with radial branching increasing towards the medial region, while their peripheral counterparts extended processes running parallel to the edges of the layer. Microglia of the granular layer were nearly always found to be more radial, and processes from different cells frequently intersected. In the white matter microglia were again more closely packed, and radially branched, while the cerebellar nuclei were most densely populated with microglia. Moving in a lateral to medial direction, microglia increased the number of primary processes and the complexity of the higher order branches so that by the cerebellar nuclei microglia often displayed quaternary structures. Because the stain used (NDPase) also labelled the vasculature, Vela et al. (1995) noted that microglia regularly contacted blood vessels. This, when considered with the increasing density of microglia in regions more populated with neurons suggested the potential for microglia to be involved in neuronal signalling.

3. Physical independence of microglia

Perhaps one of the most intriguing properties of microglia is that they are not permanently in contact with one another. In an intriguing study Jinno et al. (2007) examined the spatial distribution of Iba-1 microglia within the hippocampus using a 3D point process analysis. The results from this study demonstrated that the spatial distribution of microglia was significantly 'repulsive' (see Fig. 2). This study was first to quantitatively demonstrate the physical independence of microglia. For cells involved in monitoring, physical independence provides an optimal strategy for maximising the efficiency with which they can interrogate the interstitial space within their micro environment (Jinno et al., 2007). Further, Jinno and colleagues identified that microglial spacing was lowest in those areas of the hippocampus characterized by the highest neural activity, such as CA3, suggesting that variations in microglial density may correspond to their influence on dendritic spine stability and long term potentiation. The absence of clear connectivity with other neighbouring microglia distinguishes microglia from neurons, which are extensively linked through electro-chemical synapses, and from astrocytes, that while possessing discreet domains, exhibit are extensively connected to other astrocytes via connexin hemichanels and to the vasculature (Bushong et al., 2002; Graeber, 2010).

4. Apparent conservation of structure across species

Microglia, or cells possessing microglial-like properties, have been observed across a wide variety of species that differ quite markedly with respect to their evolutionary history (Sieger and Peri, 2013). Microglial cells, exhibiting small somas, with relatively sparse cytoplasm, and a moderate number of primary processes that are extensively branched at both the secondary and tertiary level have been observed in fish, lizards, mice, rats, primates, pigs,

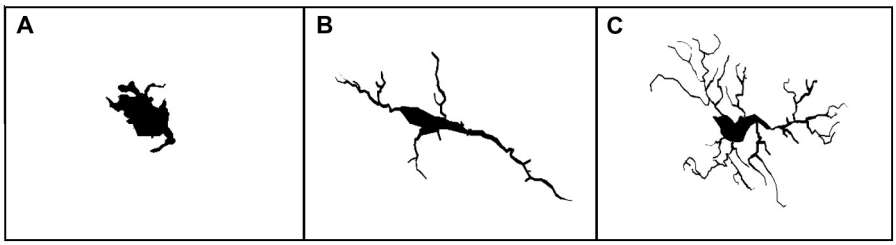

Fig. 1. Three principal forms of microglia as described by Lawson et al. (1990) in one of the first modern quantitative examinations of microglial distribution within the rodent brain. (A) Compact microglia; (B) longitudinal microglia; (C) radial microglia. These cells were identified from a systematic immunohistochemical study of the mouse brain in which tissue sections were labelled with the F4/80^{+} antibody, which putatively labels microglia within the CNS. Cells described in this study have been adapted by undertaking digital reconstructions using Neurolucida.