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Is cell migration or proliferation dominant in the formation of linear arrays of oligodendrocytes?

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HIGHLIGHTS

- Formation of linear arrays of CNS myelinating cells modelled.
- Simulation results compared to new experimental data.
- Cell migration, proliferation, differentiation and death processes incorporated.
- Proliferation necessary to increase cell number.
- Cell migration and attachment mechanism naturally creates arrays.

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ABSTRACT

Oligodendrocytes are the myelin-producing cells of the central nervous system that are responsible for electrically insulating axons to speed the propagation of electrical impulses. A striking feature of oligodendrocyte development within white matter is that the cell bodies of many oligodendrocyte progenitor cells become organised into discrete linear arrays of three or more cells before they differentiate into myelin-producing oligodendrocytes. These linear arrays align parallel to the direction of the axons within white matter tracts and are believed to play an important role in the co-ordination of myelination. Guided by experimental data on the abundance and composition of linear arrays in the corpus callosum of the postnatal mouse brain, we construct discrete and continuous models of linear array generation to specifically investigate the relative influence of cell migration, proliferation, differentiation and death of oligodendroglia upon the genesis of linear arrays during early postnatal development. We demonstrate that only models that incorporate significant cell migration can replicate all of the experimental observations on number of arrays, number of cells in arrays and total cell count of oligodendroglia within a given area of the corpus callosum. These models are also necessary to accurately reflect experimental data on the abundance of linear arrays composed of oligodendrocytes that derive from progenitors of different clonal origins.

1. Introduction

Oligodendrocytes (OLs) are the cells in the central nervous system (CNS) responsible for the myelination of axons. The long thin sheaths of myelin that wrap around segments of axons provide both electrical and physical insulation which enables fast conduction of electrical signals along axons, known as saltatory conduction (Baumann and Pham-Dinh, 2001). OLs also provide critical trophic and metabolic support of neurons (Nave, 2010; Saab et al., 2013). Interestingly, the abundance and topographic organisation of myelin differs greatly among different parts of the CNS. In the mouse, for example, almost the entire length of every axon in the optic nerve is myelinated (Dangata and Kaufman, 1997) whilst in the corpus callosum (CC), only around 30% of axonal profiles are myelinated (Sturrock, 1980). In the cerebral cortex, the axons of pyramidal cells are composed of myelinated segments interspersed with long, unmyelinated tracts rather than

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series of uninterrupted myelin internodes (Tomassy et al., 2014). Collectively these findings raise the possibility that myelinated axons in white matter tracts such as the CC could also exhibit both myelinated and unmyelinated segments along their length.

The implication that myelination is controlled in a context-dependent manner is supported by magnetic resonance imaging studies in humans which demonstrate that learning skills such as juggling or piano playing are associated with increased myelination of neuronal circuits required for that behaviour (Scholz et al., 2009; Bengtsson et al., 2005). Similarly, recent studies in mice indicate that the generation of new myelinating OLs is critical for learning a complex motor task in adulthood (McKenzie et al., 2014). A role for electrical activity within axons in regulating the process of selecting axons for myelination is becoming increasingly clear (Rahul et al., 2014; Hines et al., 2015; Mensch et al., 2015). Despite these recent advances, the cellular dynamics responsible for orchestrating the precise topographic distribution of myelin along axons within white matter remains poorly understood. Clarifying the mechanisms underlying the spatial organisation of OLs could also shed light on how myelin is regenerated after myelin loss such as in multiple sclerosis, a demyelinating disease in which OLs are killed as a result of autoimmune attack. Consequently, there is considerable interest in understanding the cellular dynamics underlying remyelination after demyelinating injury (Xing et al., 2014), as well as during brain development and ongoing adult myelin plasticity.

How then is myelin topography established within white matter? Answering this question requires careful dissection of the sequential development of OLs from oligodendrocyte progenitor cells (OPC), a highly motile and proliferative cell population that differentiates into OLs through a series of tightly coordinated stages (Mitew et al., 2014). Whilst electrical activity within axons has been demonstrated to promote OPC differentiation (Rahul et al., 2014) and to bias the selection of axons that will be myelinated (Hines et al., 2015), additional clues underlying the establishment of myelin topography have arisen from studies examining how OL patterning emerges within white matter. Röth et al. (2016) have described that OLs in white matter tracts such as the CC tend to organise themselves into linear arrays typically composed of 3–8 cells that align in parallel with the longitudinal axis of axons in the tract. These linear arrays are similar to an earlier description of rows of interfascicular OLs in the rat fimbria (Suzuki and Raisman, 1992).

Linear arrays could form, for example, through proliferation of individual, stationary OPCs prior to maturation into OLs, or through a process such as migration and attachment where unattached OPCs attach to another OPC or OL to generate arrays. Here we develop both discrete stochastic and continuous deterministic models to investigate the relative importance of cell migration, proliferation, differentiation and death for the development of these array structures in the mouse CC. Experimental data on the number of arrays, number of cells in arrays and the extent to which OLs within linear arrays in the CC derive from different clonal origins (from dorsal Emx1-specified or ventral Gsh2-specified OPCs) are used to test the relative importance of cell migration and proliferation to array formation.

The modelling supports the hypothesis that linear arrays of oligodendrocytes in the CC are primarily generated as a result of the preferential attachment of migratory OPCs. *In situ* clonal expansion also plays a role, but the preference for arrays to be of mixed clonal origin establishes that *in situ* clonal expansion is a lesser contributor than migration and attachment.

2. Biological background

Here we briefly describe the structural properties and temporal

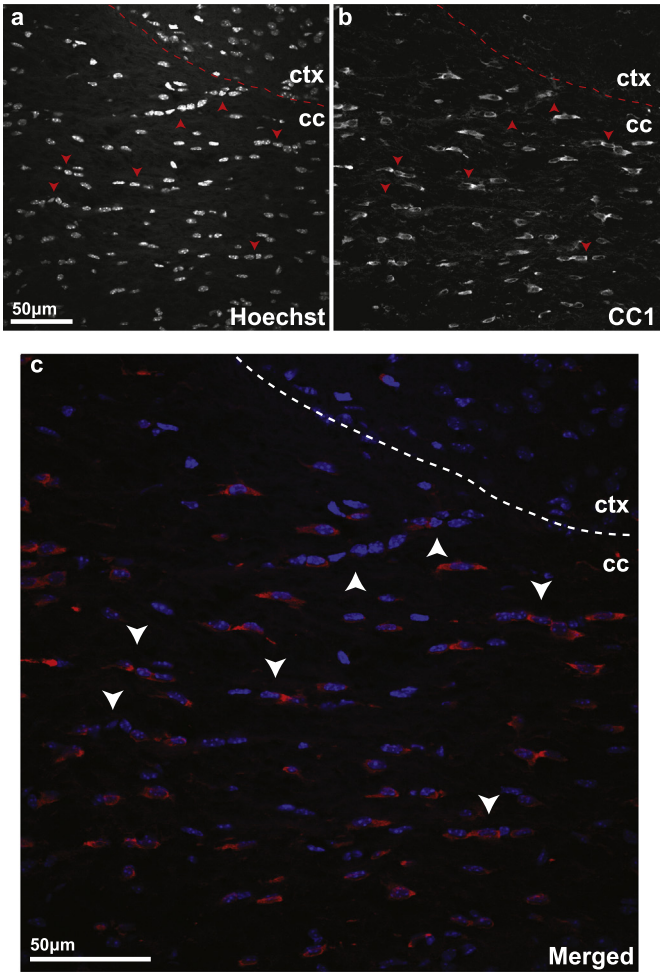

Fig. 1. Immunohistochemical image of linear arrays in the corpus callosum of a postnatal day 14 (P14) mouse sectioned in the coronal plane. (a) Labelling of cell nuclei using Hoechst dye reveals linear array structures of variable length (red arrowheads). (b) CC1-labelled cells to detect mature oligodendrocytes (red arrowheads). (c) Merged image reveals that many mature oligodendrocytes (CC1+ cells) reside within linear arrays (white arrowheads). Red dashed lines outline the border between the corpus callosum (cc) and the cortex (ctx). Scale bar = 50 μm. (For interpretation of the references to colour in this figure caption, the reader is referred to the web version of this paper.)

dynamics of linear array development in the postnatal CC of the mouse. Röth et al. (2016) define a linear array of oligodendroglia (OPCs and/or OLs) using three criteria. An array contains at least three cells (OLs, OPCs or both), the distance between cells is less than the diameter of a cell nucleus and the alignment of the array must be parallel to the axonal orientation (here taken to be horizontal). Examples of linear arrays located in the CC of a postnatal day 14 (P14) mouse brain are indicated in Fig. 1. The axons of neurons in this coronal tissue section are not visible but are orientated horizontally. A schematic of the region of interest and the alignment of OLs along axons is shown in Fig. 2.

OPCs start to migrate into the CC as early as embryonic day 16 (E16) in the first of three distinct waves that are specified in different regions of the developing forebrain. By P30, the CC contains a heterogeneous mixture of two clonally distinct populations, namely Gsh2-specified progenitors derived from the ventral forebrain and Emx1-derived progenitors derived from the dorsal forebrain (Kessaris et al., 2006). OPCs in the mouse CC continue to proliferate extensively in the early postnatal period and from P7 start to exit the cell cycle, differentiate into pre-myelinating OLs and lose their migratory capacity (Mitew et al., 2014). Pre-myelinating OLs represent a highly transient stage wherein cells that