Specification of CNS glia from neural stem cells in the embryonic neuroepithelium

Nicoletta Kessaris, Nigel Pringle and William D. Richardson*

Wolfson Institute for Biomedical Research and Department of Biology, University College London, Gower Street, London WC1E 6BT, UK

All the neurons and glial cells of the central nervous system are generated from the neuroepithelial cells in the walls of the embryonic neural tube, the 'embryonic neural stem cells'. The stem cells seem to be equivalent to the so-called 'radial glial cells', which for many years had been regarded as a specialized type of glial cell. These radial cells generate different classes of neurons in a position-dependent manner. They then switch to producing glial cells (oligodendrocytes and astrocytes). It is not known what drives the neuron–glial switch, although downregulation of pro-neural basic helix–loop–helix transcription factors is one important step. This drives the stem cells from a neurogenic towards a gliogenic mode. The stem cells then choose between developing as oligodendrocytes or astrocytes, of which there might be intrinsically different subclasses. This review focuses on the different extracellular signals and intracellular responses that influence glial generation and the choice between oligodendrocyte and astrocyte fates.

Keywords: CNS; oligodendrocyte; astrocyte; development

1. Introduction

The nervous system is composed of neurons and glial cells. Glial cells in the central nervous system (CNS) include both the 'macroglia', which are derived from the neural tube, and the 'microglia', which are derived from haemopoietic precursors. Microglia are the resident macrophages of the CNS and play a key role in immune surveillance and defence. This review is concerned with the two major classes of macroglia: astrocytes and oligodendrocytes. These cells were first visualized over a century ago (Andriezen 1893) and were given names that described their morphology in Golgi tissue preparations: astrocytes ('star-like') and oligodendrocytes ('sparsely branching'). The term 'glial' originally referred to the sticky nature of the substance we now know as white matter, the myelinated axon tracts. This seeded the idea that glial cells, which are abundant in white matter, have a purely passive support role—the 'glue' holding the neurons together (for a historical review see Pasik & Pasik 2004). Today, it is recognized that glial cells play active roles in nervous system function, even forming synaptic contacts with neurons and contributing in some way to information storage or processing. Oligodendrocytes have a well-defined function—formation of the insulating myelin sheaths around CNS axons—but they and their precursors also express voltage- and ligand-gated ion channels and have synaptic input from neurons. Astrocytes have many described functions: (i) they provide structural and trophic support for neurons, (ii) they interact intimately with blood vessels and induce formation of the blood–brain barrier, and (iii) they regulate CNS synaptogenesis and synaptic trans-

cells (Raff et al. 1983), at which time they were named oligodendrocyte-type-2 astrocyte progenitor cells (O-2A progenitors) to denote the fact that they can differentiate into either oligodendrocytes or astrocytes (type-2 subtype), depending on the culture medium. However, it has so far not proved possible to identify cells with the antigenic phenotype of type-2 astrocytes in vivo, so the precursor cells are now more usually referred to simply as oligodendrocyte precursor or progenitor cells (OLPs or OPCs (OLP used herein)). These go through several identifiable maturation stages characterized by distinct morphological and antigenic changes, before finally associating with axons and elaborating myelin. Since mature myelinating oligodendrocytes are ubiquitous throughout the mature CNS, they were originally presumed to be derived more-or-less equally from all parts of the embryonic germinal zones—the so-called ventricular zone (VZ) that surrounds the ventricles of the brain and the central canal of the spinal cord. However, with the discovery of early markers of the oligodendrocyte lineage, such as the platelet-derived growth factor receptor-alpha (Pdgfr-α; Pringle & Richardson 1993), the myelin proteolipid protein isoform DM20 (Timsit et al. 1995) and the O4 antigen (Noll & Miller 1993), came the realization that OLPs might be generated from defined, spatially localized subsets of NEPs.

In the spinal cord, the first OLPs are generated from ventral NEPs (Warf et al. 1991; Noll & Miller 1993; Pringle & Richardson 1993; Yu et al. 1994; Timsit et al. 1995) from a specific domain of the VZ called pMN that also generates motor neurons (MNs; Richardson et al. 1997; Sun et al. 1998; Lu et al. 2002; Takebayashi et al. 2002; Zhou & Anderson 2002). The proliferating OLPs migrate away and rapidly populate the entire spinal cord before differentiating into myelin-forming oligodendrocytes. Recent studies using mouse mutants that lack this ventral source of OLPs showed that dorsal NEPs also generate some OLPs (Cai et al. 2005; Vallstedt et al. 2005). This was confirmed by Cre-lox fate mapping in wild-type mice (Fogarty et al. 2005). The dorsal half of the spinal cord neuroepithelium contributes approximately 20% of all oligodendrocytes in the cervical spinal cord and up to 50% of the oligodendrocytes in the dorsal funiculus (dorsal axon tracts; Fogarty (2005); for a review see Richardson et al. (2006); figure 1). In the mouse, the dorsally derived OLPs start to appear around embryonic day 15, approximately 2 days later than their ventrally derived counterparts. When they first appear, they have a distinctive radial morphology and co-label with the radial glial marker RC2 (Fogarty et al. 2005), verifying previous suggestions that oligodendrocytes as well as astrocytes might form by direct transformation of radial glia (Choi et al. 1983; Hirano & Goldman 1988; Voigt 1989; Culican et al. 1990; Barry & McDermott 2005).

A similar theme is observed at more anterior levels of the neuraxis. In the forebrain, the first Pdgfr-α-positive OLPs appear in the ventral neuroepithelium (anterior entopeduncular area, AEP; medial ganglionic eminence, MGE), then spread throughout the forebrain by migration and proliferation (Spassky et al. 1998; Olivier et al. 2001; Spassky et al. 2001; Tekki-Kessaris et al. 2001). Subsequent waves of OLP generation emanate from more dorsal regions (the lateral and the caudal ganglionic eminences (LGE/CGE)) and finally from within the cortex (Kessaris et al. 2006). Thus, there is a progressive wave of OLP production from ventral to dorsal regions (figure 1). The very first OLPs generated in the ventral forebrain (MGE/AEP) almost disappear during post-natal life and are replaced by other populations including the LGE/CGE-derived population. This might reflect some selective advantage of more recently generated OLPs that leads to competitive elimination of ventrally derived cells. Alternatively, continual turnover (loss and replacement) of oligodendrocytes during adult life might lead to gradual loss of the MGE/AEP-derived population because stem cells in the adult subventricular zone (SVZ)—the ultimate source of new oligodendrocytes in the adult (Levison & Goldman

helix–loop–helix (bHLH) transcription factor genes, which have been classified as either class I or class II depending on whether they are activated (class II) or repressed (class I) by Shh (Briscoe et al. 2000). The combinatorial expression of these genes defines progenitor domains along the dorsal–ventral axis and influences the neuronal subtypes they generate. Shh is thus essential for the generation of different classes of ventral spinal cord neurons. Several studies have shown that Shh also promotes the generation of pMN-derived OLPs in the spinal cord (Poncet et al. 1996; Pringle et al. 1996; Orentas et al. 1999) and is a potent inducer of OLP formation in primary cultures of dissociated forebrain NEPs (Tekki-Kessaris et al. 2001; Kessaris et al. 2004). In the absence of Shh signalling, ventrally derived OLPs fail to form in the spinal cord or forebrain (Orentas et al. 1999; Nery et al. 2001; Tekki-Kessaris et al. 2001). Furthermore, transplanting Shh-expressing tissue adjacent to the dorsal neural tube in vivot to-0.4 TD[(in)-5]TJ]TJ6(is.6487 0 TDD(Oreh-e)-17.4(s)-614&ral)-513Mill(the5K)-12.8(1996

conversely, inhibition of BMPs with the BMP antagonist Noggin causes an expansion of the oligodendrogenic domain. The same effect is also caused by surgical removal of the roof plate (Mekki-Dauriac et al. 2002). In all these experiments, effects on OLP and astrocyte production are reciprocal (see §3). Collectively, the data suggest that endogenous BMP signals spatially restrict neurogenesis and oligodendrogenesis to defined neuroepithelial regions (Hall & Miller 2004).

maintenance of the pMN pool for subsequent generation of oligodendrocytes (Lee et al. 2005). Although Olig2 is expressed in MN precursors, its expression is downregulated in differentiating MNs. Unlike proneural proteins and other bHLH transcription factors, which mostly act as transcriptional activators, Olig2 appears to function as a transcriptional repressor (Bertrand et al. 2002). Direct targets of Olig2 presumably include MN determinants (Lee et al. 2005) and astrocyte specification factors (see §3), although such targets are as yet poorly characterized.

Unlike Olig2, which seems to have essential roles in oligodendrocyte development, initial evidence indicated a redundant, non-essential function for Olig1. Mice lacking Olig1 showed a slight delay in oligodendrocyte maturation but were otherwise normal. By contrast, Olig2 mutant mice lacked all oligodendrocytes and MNs in the spinal cord (Lu et al. 2002), although oligodendrogenesis in the fore- and hindbrain was apparently normal. However, more recent work with the Olig1 mutant mice questions the previous data and suggests that Olig1 is in fact a central regulator of oligodendrocyte maturation and myelinogenesis (Xin et al. 2005). These authors found that, in the absence of Olig1, the mice developed severe neurological deficits and died within the third post-natal week. While oligodendrocyte progenitors developed normally, maturation was severely affected and markers of myelinating oligodendrocytes were absent. Although the reason for the discrepancies in different loss-of-function studies is not clear, all data support a functional role for Olig1 in oligodendrocyte maturation. This is also consistent with the recent striking finding that remyelination does not occur in Olig1 null adult mice with experimentally induced focal demyelination (Arnett et al. 2004).

Another bHLH gene that has recently been found to play a role in oligodendrocyte development is the proneural gene Mash1 (Parras et al. 2004). In the early telencephalon, Mash1 is co-expressed with Olig2 at the time of oligodendrocyte specification in the MGE/AEP and its expression is briefly maintained in initial populations of migrating OLPs (Parras et al. 2005). At later stages, Mash1-negative OLPs populate the telencephalon. In newborn mice, expression of Mash1 can be observed in a large fraction of OLPs, and Mash1-deficient pups have severely reduced numbers of oligodendrocytes in the olfactory bulb (Parras et al.

genes (Stolt et al. 2005). The loss of Sox10, on the other hand, results in normal numbers of oligodendrocyte progenitors but a failure to mature, indicating that Sox10 is required for terminal differentiation (Stolt et al. 2002).

(d) ***Oligodendrocyte diversity?***

Oligodendrocyte heterogeneity has been reported on the basis of morphology and the observation that mature cells myelinate either a single large diameter axon or several small axons (Bunge 1968; Bjartmar et al. 1994; Butt et al. 1997). It is not clear whether this variation reflects intrinsic differences among oligodendrocyte subtypes or phenotypic plasticity. Heterogeneity has also been proposed on the basis of expression of markers such as Pdgfra or PLP/DM20 (Le Bras et al. 2005). The possibility that there might be different functional subclasses of oligodendrocyte becomes more intriguing owing to the discovery of dorsally derived as well as ventrally derived OLPs and the likelihood that these are specified by different signals (Chandran et al. 2003; Kessaris et al. 2004). Therefore, a major question in the field is whether different signalling pathways generate different oligodendrocyte subtypes. An attempt was made to address

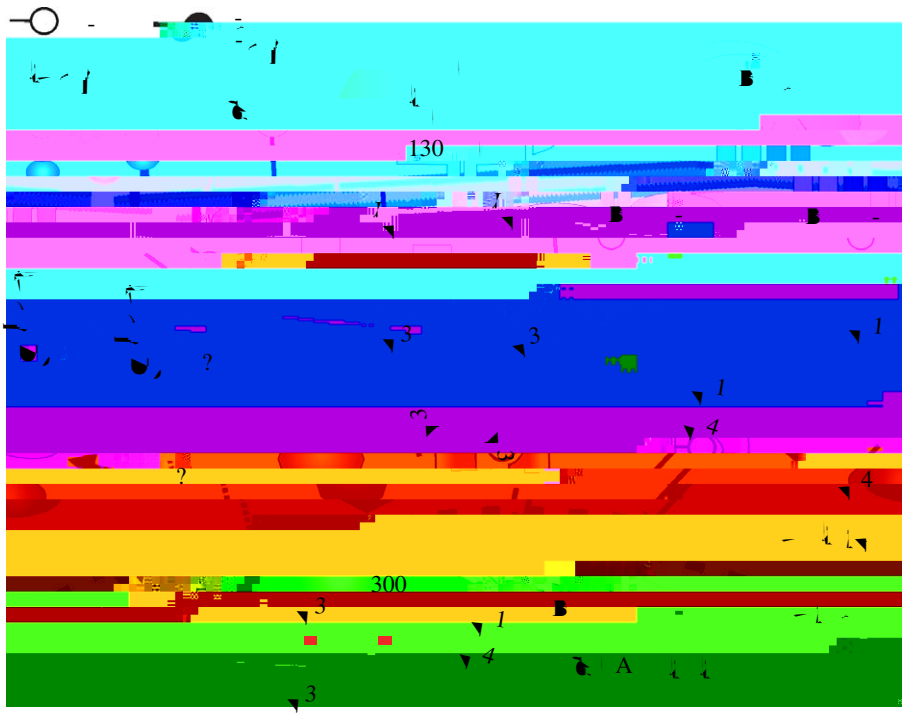

Figure 2. Signalling pathways involved in the induction of astrocyte specification/differentiation. Astrocyte differentiation is thought to be induced via cytokine and/or BMP signalling pathways. Cytokines (LIF or CNTF) induce dimerization of the LIF receptor (LIFR) with co-receptor gp130, leading to phosphorylation and activation of Janus kinases (Jaks). Receptor dimerization also creates docking sites for the transcription factor Stat3, which is tyrosine phosphorylated by Jaks. The phosphorylated Stats dimerize and move into the nucleus, recruiting p300 and binding to specific sequences in the GFAP promoter. BMP dimers induce the tetramerization of the BMPR-I and BMPR-II receptors, which are serine–threonine kinases. BMPR-II then phosphorylates and activates BMPR-I, which phosphorylates Smad1. Phosphorylated Smad1 associates with Smad4 (unknown stoichiometry) and the complex moves into the nucleus, recruiting p300 and CBP, which probably bind directly to the GFAP promoter and initiate transcription. Smads and Stats bind opposite ends of p300, which presumably allows synergistic integration of LIF/CNTF and BMP signalling pathways. These signalling pathways can be inhibited by neurogenins, which are thought to act by blocking Stat dimerization and also by sequestering p300. The activity of neurogenin can be inhibited, in an undefined manner, by growth hormone. Notch signalling (via the cleaved/released intracellular domain) might

whether the two phenotypes can be assigned to GFAP-positive and GFAP-negative molecular subgroups and so on. Some of the controversies might be attributable to different methodologies, regional variation, the criteria according to which cells were selected for recording (e.g. on the basis of morphology) and the bias that this might introduce (Steinhauser et al. 1992; Matthias et al. 2003; for review see Walz 2000). It is also possible that the passive and complex subtypes can interconvert rapidly and this might be influenced by the way cells or tissue slices are treated prior to and during recording. An additional complication results from the fact that astrocytes are extensively coupled via gap junctions in vivo, which tends to linearize current–voltage relationships (passive phenotype). A recent study concluded that the complex pattern is found only during early post-natal development and that most or all astrocytes in the mature hippocampus are of the passive variety (Zhou et al. 2006). This suggests that complex astrocytes might be glial precursors, and passive astrocytes their differentiated progeny.

It should be clear from the above discussion that, when seeking to define the mechanisms of astrocyte specification and subsequent development, we are on uncertain ground. As long as we remain unsure whether astrocytes comprise one group of phenotypically plastic cells or several intrinsically distinct subgroups, it will be difficult to know whether different laboratories are studying the same or different developmental pathways. In practice, most workers rely on induction of GFAP expression in vivo or in neural cell cultures as a surrogate for astrocyte specification. This raises additional questions about whether we are all studying normal developmental mechanisms (astrogenesis) or the acute activation of GFAP expression that accompanies CNS injury or disease (astrocytosis).

(b) ***The embryonic origins of astrocytes***

Astrocytes, like oligodendrocytes and neurons, are ultimately formed from the NEPs that line the lumen of the embryonic neural tube. However, there is a persuasive body of evidence that astrocytes—at least fibrous astrocytes—are formed indirectly from NEPs via radial glial cells. The evidence supporting this idea was largely circumstantial. First, immunohistochemical studies have identified cells with antigenic and morphological phenotypes intermediate between radial glia and astrocytes (Choi et al. 1983; Hirano & Goldman 1988; Voigt 1989; Barry & McDermott 2005). Second, radial glial cells begin to disappear during development at about the same time as astrocytes appear (Choi & Lapham 1978; Schmechel & Rakic 1979; Misson et al. 1988) and the cells

interpreted as intermediate forms are also observed during this period. Recently, more direct evidence has come from genetic fate mapping experiments. When introduced into transgenic mice, a short promoter fragment from the human GFAP gene drives reporter gene expression not only in differentiated astrocytes, but also earlier in radial glia. When these radial glia were purified from transgenic brains and cultured *in vitro*, they gave rise to astrocytes as well as neurons, providing the first indication that radial glia can be pluripotent NPCs (Malatesta *et al.* 2000). It has now been confirmed that radial glia are also pluripotent precursors *in vivo* (Noctor *et al.* 2002; Malatesta *et al.* 2003; Anthony *et al.* 2004; Fogarty *et al.* 2005).

It is not known whether all astrocytes are generated directly from radial glia. It is also not known whether all radial glia generate astrocytes, or whether they generate different subtypes of astrocytes from different parts of the VZ. In the embryonic spinal cord, oligodendrocytes and astrocytes are generated preferentially from different parts of the VZ, with most oligodendrocytes being derived from the pMN domain (Sun *et al.* 1998; Lu *et al.* 2002; Takebayashi *et al.* 2002; Zhou & Anderson 2002). Other progenitor domains generate predominantly astrocytes (Pringle *et al.* 1998; Lu *et al.* 2002; Pringle *et al.* 2003; Fogarty *et al.* 2005). By Cre-*lox* fate mapping in mice, we showed that the *Dbx1*-expressing domain (p1, p0, dP6 and dP5—four progenitor domains centred on the dorsoventral midline) generates significant numbers of protoplasmic astrocytes, the majority of which lie in grey matter and do not express detectable GFAP immuno-reactivity. The *Dbx1* domain also generates fibrous astrocytes in the white matter and a small number of oligodendrocytes, in addition to neurons (Fogarty *et al.* 2005). Furthermore, the *Nkx2.2*-expressing domain (p3, the ventral-most domain abutting the floor plate) generates protoplasmic and fibrous astrocytes in addition to neurons and small numbers of oligodendrocytes (R.Taveira-Marques, N. Kessaris & W. D. Richardson 2006, unpublished observations). The protoplasmic astrocytes that are generated from *Dbx1* and *Nkx2.2* domains are morphologically similar, but occupy different territories in the adult spinal cord. It remains to be determined whether they are functionally or physiologically distinguishable.

(c) *Astrocyte specification*

As discussed previously, oligodendrocyte specification in the ventral spinal cord and telencephalon relies on the induction of *Olig* gene expression by Shh. A hedgehog-independent, FGF-dependent mechanism of *Olig* gene induction and oligodendrocyte specification has also been identified. What are the extracellular signals and cell-intrinsic factors that specify astrocytes? Two principal signalling systems have been identified: (i) the BMPs and (ii) cytokines such as

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p300 bridges Stat3 and Smad1. They discovered that

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