AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823
(Some corrections may occur before final publication online and in print)

Annu. Rev. Neurosci. 2002. 25:471–90
DOI: 10.1146/annurev.neuro.25.030702.130823

THE ROLE OF NOTCH IN PROMOTING GLIAL AND NEURAL STEM CELL FATES

Nicholas Gaiano[1,2] and Gord Fishell[1]

[1]*Developmental Genetics Program, and Department of Cell Biology, Skirball Institute of Biomolecular Medicine, New York University School of Medicine, New York, NY 10016; e-mail: fishell@saturn.med.nyu.edu*

[2]*Current address: Departments of Neurology and Neurosciences, Institute for Cell Engineering, Johns Hopkins University School of Medicine, Baltimore, Maryland 21287; e-mail: ngaiano@jhmi.edu*

Key Words cell-fate specification, gliogenesis, radial glia, *Drosophila*, vertebrate

■ **Abstract** The Notch signaling pathway has long been known to influence cell fate in the developing nervous system. However, this pathway has generally been thought to inhibit the specification of certain cell types in favor of others, or to simply maintain a progenitor pool. Recently, this view has been challenged by numerous studies suggesting that Notch may play an instructive role in promoting glial development. This work has inspired a new look at the role of Notch signaling in specifying cell fate. It has also prompted further consideration of the emerging view that in some contexts glia may be multipotent progenitors. This review examines the role of Notch during gliogenesis in both fruit flies and vertebrates, as well as evidence in vertebrates that some glia may be stem cells.

INTRODUCTION

The Notch/Delta signaling pathway is highly conserved across species and is widely used during both vertebrate and invertebrate development to regulate cell fate in the developing embryo (Artavanis-Tsakonas et al. 1999, Lewis 1998). The Notch family of proteins are cell-surface receptors that are activated by the ligands Delta and Jagged (Serrate is the fly homologue of Jagged). Both the receptors and ligands are single-pass transmembrane proteins, which suggests that signaling through the Notch receptor requires cell-cell contact. Upon ligand binding the intracellular portion of the Notch receptor is cleaved and enters the nucleus, where it influences the expression of numerous transcription factors. A great deal of research has been focused on understanding how the Notch signal is transmitted and regulated on the molecular level (Mumm & Kopan 2000, Weinmaster, 1997). In addition, many studies have examined the role of the Notch pathway during the development of nonneural tissues, such as the somites (Barrantes et al. 1999, Jiang et al. 2000), the limbs (Irvine & Vogt 1997, Vargesson et al. 1998), and the

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

immune system (Anderson et al. 2001, Osborne & Miele 1999). For the purposes of this review, however, these issues are not considered further, and instead the role of Notch signaling on a cellular level during neural development is discussed.

Much of the initial understanding of the Notch pathway came from studies in worms and flies. In these systems, Notch was found to influence fate choices between cells with equivalent developmental potential. For example, in the worm vulva, although two cells have the potential to become a specialized cell type called the anchor cell, the Notch homologue lin-12 ensures that only one does, while the other becomes a ventral uterine precursor (Seydoux & Greenwald 1989, Sternberg & Horvitz 1989). Similarly, in flies, Notch influences the fate of cells in both the central nervous system (CNS) and peripheral nervous system (PNS). For instance, Notch is used to identify a single cell, among a small cluster of equivalent cells, to become either a neuroblast (also called neuroglioblast) in the CNS (Artavanis-Tsakonas et al. 1991), or a sensory organ precursor (SOP) in the PNS (Furukawa et al. 1992, Schweisguth 1995, Schweisguth & Posakony 1992). Subsequently, Notch signaling is used to regulate the acquisition of distinct fates by the daughter cells of neuroblasts and SOPs (Guo et al. 1996). Thus, in both the worm vulva and fly nervous system, Notch influences the decision between alternative cell fates.

The mechanism by which neuroblasts and SOPs are specified in the fly ectoderm has strongly influenced our view of the role of Notch in the vertebrate CNS. During vertebrate neural development, the canonical view has been that Notch signaling is used to maintain a pool of uncommitted precursors, while a subset of cells are selected to leave this pool and differentiate into neurons (Lewis 1996). This balance between progenitor maintenance and neuronal differentiation allows the continuous generation of neurons throughout development and permits temporal control over the specification of distinct neuronal fates. The common theme between neuroblast selection in flies and the selection of cells to undergo neuronal differentiation in the progenitor pool of vertebrates is that Notch activity inhibits the surrounding cells from becoming the primary cell type being specified.

The apparent tendency of Notch to inhibit differentiation has suggested that this pathway is an indirect regulator of cell fate, rather than a direct or "instructive" regulator. The widespread use of Notch signaling to influence the specification of many different cell fates during development has further suggested that Notch is unlikely to instructively influence these fates. Recently, however, numerous studies in vertebrates have suggested that rather than simply inhibiting neuronal differentiation and maintaining a neural progenitor state, Notch may, in some contexts, promote the acquisition of glial identity (Furukawa et al. 2000, Gaiano et al. 2000, Hojo et al. 2000, Morrison et al. 2000, Scheer et al. 2001). This work has found that Notch can actively direct cells toward certain fates and thereby has called for a re-evaluation of Notch's potential role as an instructive signal during development.

In this review the role of Notch during gliogenesis in both flies and vertebrates is examined. Though it is clear that Notch signaling influences gliogenesis across species, there is no uniform instructive role for Notch during this process. Depending upon the context, Notch can either promote or inhibit gliogenesis. It is

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

interesting that in some cases Notch signaling in vertebrates promotes glial cell types that may retain progenitor character. This work suggests that, in certain contexts, Notch can maintain progenitor identity, consistent with the traditional view but that these progenitors acquire glial characteristics. In addition to an overview of the role of Notch during gliogenesis, the evidence is discussed that certain glial cell types, which are promoted by Notch signaling (i.e., radial glia, astrocytes, Müller glia), may be multipotent progenitors.

NOTCH DURING GLIOGENESIS IN FLIES

In the fruit fly, CNS and PNS progenitors are ectodermally derived (Campos-Ortega 1993, Jan & Jan 1994, Modolell 1997) (Figure 1*a*). The expression domains of both dorsal/ventral and anterior/posterior patterning genes define groups of 4–7 cells termed proneural clusters (Bhat 1999, Jan & Jan 1994). These cells express the proneural genes of the *achaete-scute* complex and *atonal*, which encode basic helix loop helix transcription factors that impart a neural ground state to ectodermal cells (Campos-Ortega 1993, Modolell 1997, Skeath & Doe 1996). Although all cells in a proneural cluster have the potential to give rise to neural cell types, normally only one cell in each is specified to become a neuroblast in the CNS, or an SOP in the PNS. This specification is achieved through cell-cell signaling, and is mediated by the Notch pathway. The cell that becomes the neuroblast or the SOP expresses the highest levels of the Notch ligand Delta, thus activating Notch in the surrounding cells, inhibiting their differentiation into neuroblasts or SOPs. This inhibition is achieved, at least in part, through the downregulation of proneural genes by Notch activity. In the absence of Notch signaling, all of the cells in a cluster continue to express proneural genes and become neuroblasts or SOPs, a circumstance that leads to the neurogenic phenotype characteristic of mutations in the Notch pathway (Jan & Jan 1994, Knust & Campos-Ortega 1989, Xu et al. 1990). The selection of neural progenitors is only the first of Notch's roles in generating neural cell diversity in the fly. Notch signaling is also used to regulate binary fate choices during the expansion of the neuroblast and SOP lineages (Doe & Skeath 1996, Guo et al. 1996). Among the many fate choices influenced by Notch in the fly nervous system, the role of this pathway during glial specification is focused on below.

The Fly CNS

Notch has been found to influence the generation of CNS glia in flies at several stages. First, as described above, the specification of a single neuroblast in each proneural cluster is controlled by Notch (Figure 1*a*). In specific CNS clusters, the cell that delaminates will give rise only to glia and is therefore called a glioblast (Jacobs et al. 1989). In Notch mutants, the inability to select a single "blast" cell from each proneural cluster results in the generation of supernumerary glioblasts. Consequently, extra glia are generated, which suggests that Notch represses glial

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

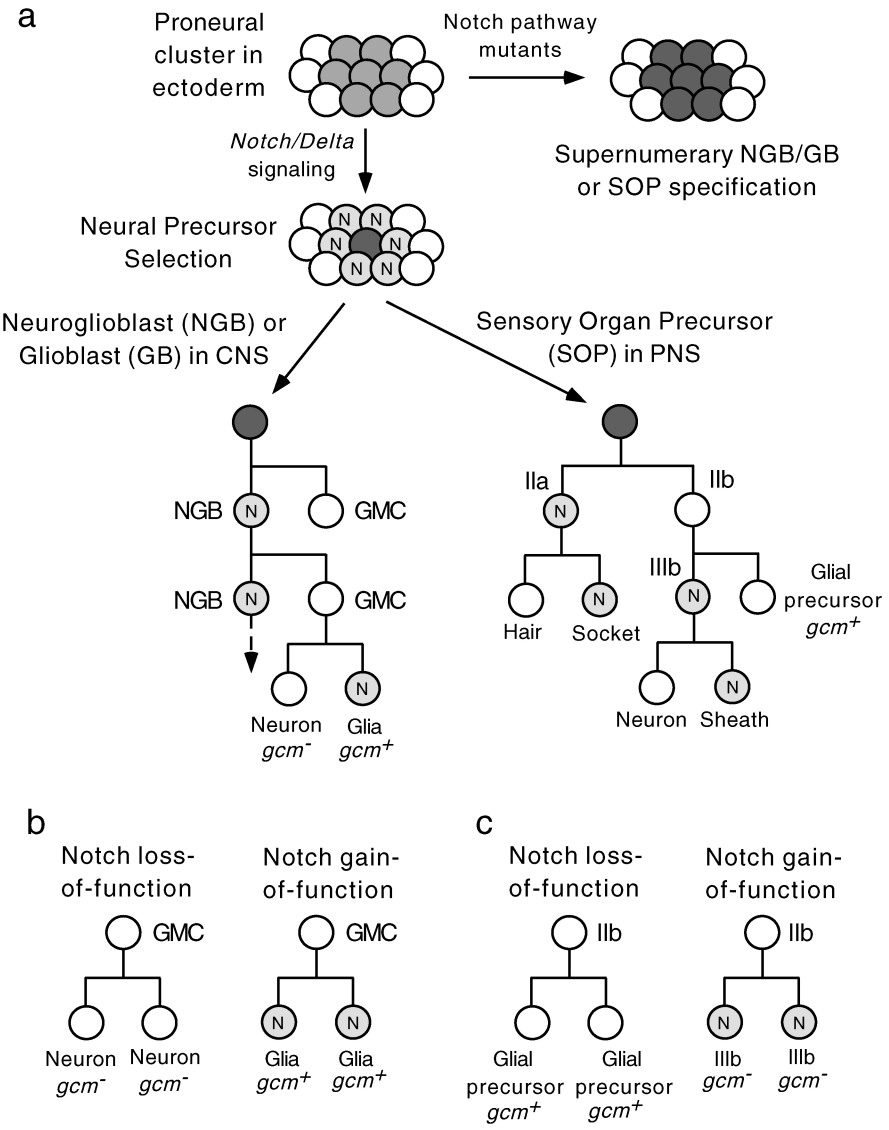

Figure 1 Role of Notch during cell-fate specification in the fly CNS and PNS. (*a*) Selection of neural precursors (*dark gray*) from proneural clusters (*medium gray*) using Notch signaling. Cells with "N" are receiving Notch signaling (*light gray*). *Left*, in the CNS the selected cell undergoes multiple rounds of self-renewing division, while also generating ganglion mother cells (GMCs). *Right*, in the PNS the SOP produces numerous cell types including a glial precursor. (*b*) Notch activity controls the GMC neuronal-glial fate choice through *glial cells missing* (*gcm*) (see Udolph et al. 2001). (*c*) Notch activity controls the IIIb-glial precursor fate choice through *gcm* (see Van De Bor & Giangrande 2001).

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

fate in this context. Strictly speaking this is true, but the role of Notch with respect to specifying glia is not specific because Notch limits the number of glioblasts or neuroblasts, depending on the proneural cluster, via the same mechanism. In support of a nonspecific function of Notch, it has also been found that Notch activity limits the delamination of the nonneural oenocyte precursors from ectoderm in the same manner (Hartenstein et al. 1992).

Recent work in the CNS has uncovered a more specific role for Notch during the decision to acquire glial identity (Udolph et al. 2001). After delamination from the ectoderm, most neuroblasts undergo a series of self-renewing divisions that also produce cells called ganglion mother cells (GMCs) (Figure 1*a*, *left*). GMCs divide again and typically give rise to one neuronal daughter and one glial daughter. In a recent study, Udolph et al. (2001) examined the role of Notch during this neuronal-glial fate choice and found Notch activity to be essential for this asymmetric division (Figure 1*b*). Specifically, this work examined the generation of the subperineurial glia (SPG) and showed that the loss of Notch function led to SPG loss and a concomitant increase in neuron number in this lineage.

To determine if Notch is sufficient to specify SPG fate, the authors examined the effect of increased Notch function, using either a mutation in Numb (a negative regulator of Notch) or by expression of a constitutively active form of Notch (ActN). Consistent with the loss-of-function result, increased Notch activity led to additional glia at the expense of neurons (Figure 1*b*). Both the loss-of-function and gain-of-function effects appeared to be mediated through the expression of *glial cells missing* (*gcm*), a gene believed to play an instructive role in the neuronal-glial fate choice throughout the embryo (Hosoya et al. 1995, Jones et al. 1995, Vincent et al. 1996). The authors examined the expression of *gcm* in the SPG lineage and found that *gcm* was normally expressed in the GMC daughter destined to become the SPG. In Notch mutants, *gcm* was not expressed in these cells (Figure 1*b*). In contrast, Notch activity in both daughters led to *gcm* expression in both, and extra glia at the expense of neurons. These data are consistent with the notion that Notch can play an instructive role during glial specification. However, it is important to note that in *gcm* mutants, activation of Notch did not promote SPG identity, which indicates that at least part of the "instructive" role of *Notch* in this context is mediated through its effect on *gcm* expression (Udolph et al. 2001).

The Fly PNS

The development of sensory organs in the fly PNS occurs in a stereotypic pattern after the specification of SOPs (Jan & Jan 1994) (Figure 1*a*, *right*). In the classically described lineage, each SOP divides into two cells, termed IIa and IIb. These cells each divide again to give rise to the hair and socket cells (IIa), and neuron and sheath cells (IIb). Analysis of the Notch pathway in the SOP lineage has proven quite useful for understanding the role of Notch during cell-fate specification. These studies utilized temperature-sensitive alleles, as well as mutations that either blocked or enhanced Notch signaling, to demonstrate that Notch has sequential

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

roles during the expansion of the SOP lineage into four distinct daughter cells. Specifically, in the SOP division, Notch is needed for specification of the IIa cell, and in the second round of divisions Notch is needed for specification the socket cell (from IIa) and the sheath cell (from IIb). Although Notch activity in the SOP lineage is clearly required to generate specific cellular fates, this work has not been widely interpreted to suggest that Notch plays an instructive role in this context. Depending on the timing of Notch activation, different cell fates are specified, which is inconsistent with the idea that Notch provides specific cell fate instruction.

More recently, the SOP lineage that gives rise to the mechanosensory bristle in the adult has been shown to include a fifth cell type, that of a glial precursor (GP) (Gho et al. 1999, Reddy & Rodrigues 1999, Van De Bor et al. 2000; Figure 1*a*, *right*). After the first SOP division to generate the IIa and IIb cells, IIb divides again to generate two cells, IIIb and a GP, which migrates away from the group and gives rise to numerous glia. IIIb then divides to give rise to the neuron and sheath cells formerly believed to be derived directly from IIb. The fact that the GP cell type has only recently been identified is likely a function of its migration away from the cluster, and the recent advent of time-lapse video microscopy.

Initial evidence that the Notch pathway might influence specification of the SOP GP came from the observation that Numb protein is segregated into this cell (Gho et al. 1999). As mentioned above, Numb antagonizes Notch signaling, which suggests that reduced Notch activity is required to acquire GP identity. Further work by Van De Bor & Giangrande (2001) has demonstrated this point convincingly. This study examined the effect of altering the Notch pathway in this lineage, using both loss-of-function and gain-of-function approaches. They found that a reduction in Notch signaling led to an increase in the number of GPs in SOP clusters, at the expense of other cell types, and that enhancing Notch activity led to a reduction in the number of GPs (Figure 1*c*).

Similar to the results described above for SPG development in the CNS, Notch was found to affect *gcm* expression in the SOP lineage (Van De Bor & Giangrande 2001). However, in contrast to the SPG lineage, where Notch positively regulated *gcm*, Notch negatively regulated this gene in the wing SOP. Therefore, in both lineages, the influence of Notch is mediated through regulation of *gcm* expression. Remarkably, however, Notch has opposite effects on *gcm* expression in these two contexts. This observation clearly suggests that attributing a uniform instructive function to Notch with respect to glial development in flies is not possible. Instead, Notch appears to behave in a context-dependent manner. The consequence of Notch activity is likely dictated by the developmental state of the cells in question, as well as other extrinsic cues they receive.

NOTCH DURING GLIOGENESIS IN VERTEBRATES

Over the course of the past decade four different Notch receptors, numerous forms of the ligands Delta and Jagged, and a variety of other Notch pathway members have been identified in vertebrates (Artavanis-Tsakonas et al. 1999, Lewis 1998,

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

Weinmaster 1997). During this time, it has become apparent that the Notch pathway functions in vertebrates in a manner similar to that observed in flies. Early evidence that Notch could inhibit neuronal differentiation in vertebrates came from in vitro work in the embryonic carcinoma cell line (P)19 cells. Under certain conditions these cells can be prompted to differentiate into neurons, astrocytes, or myoblasts. By introducing an active form of Notch (ActN) into P19 cells, Nye et al. (1994) showed that Notch could inhibit the differentiation of these cells into neurons and myoblasts. This inhibition was consistent with the action of Notch in invertebrates, as well as with an earlier study in frogs that suggested an inhibitory role for Notch in vertebrate cell-fate specification (Coffman et al. 1993). However, unexpectedly, in the P19 study ActN did not inhibit astrocyte differentiation. The authors concluded that glial fate, unlike the neuronal and myoblast fates, was refractory to Notch inhibition.

More recent work has suggested that the role of Notch during vertebrate gliogenesis is more complex than initially observed by Nye et al. (1994). Numerous studies have found that rather than simply not inhibiting gliogenesis, Notch may actively promote certain glial fates. Such fates include those of astrocytes, radial glia in the forebrain and cerebellum, Müller glia in the retina, and Schwann cells in the neural crest (each discussed below). It is interesting that in contrast, Notch has been found to inhibit oligodendrogliogenesis in the optic nerve. These studies suggest that, as in the fly nervous system, the role of Notch during vertebrate gliogenesis is not uniform.

Müller Glia

One of the first studies to suggest that Notch might actively influence glial fate in vertebrates was performed in the retina. Dorsky et al. (1995) found that the last cells to express Notch in the frog retina became Müller glia. The authors postulated that in retinal precursors Notch activation inhibited the acquisition of early born cell types, in favor of the later born Müller glia. When ActN was introduced into the retina however, even Müller glial fate was inhibited, and the ActN-expressing cells were quiescent with a neuroepithelial morphology. Taken together, these results suggested that prolonged expression of the Notch receptor led cells toward an eventual glial fate, but that the final acquisition of that fate required downregulation of Notch activity. In this case, Notch did not appear to be acting in an instructive manner, although the possibility that transient Notch activity specified a pre–Müller glial state, which could differentiate only after downregulation of Notch, could not be ruled out.Subsequently, Bao et al. (1997) examined the role of Notch in the rat retina. In contrast to the frog study, however, this work found that cells expressing ActN were proliferatively active and acquired morphologies akin to Müller glia. More recent analysis by the same group has confirmed that ActN-expressing cells express Müller glial markers, and that expression of Hes-1, a downstream effector of Notch, can also promote Müller glial identity (Furukawa et al. 2000). The *Hes* genes are basic helix loop helix transcriptional repressors that may inhibit the

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

activity of proneural transcription factors, such as Mash1 and Neurogenin2, which have recently been found to promote neurogenesis and block gliogenesis (Nieto et al. 2001, Sun et al. 2001). Consistent with the gain-of-function result described above, expression of a dominant negative form of Hes-1 blocked Müller glial fate, indicating that Notch signaling is necessary to attain this fate (Furukawa et al. 2000). Interestingly, the authors of this study suggested that the cell fate promoted by Notch signaling might represent "a hitherto undescribed population of persisting adult progenitor cells whose morphology and gene expression overlap considerably with those of Müller glia." This notion is supported by recent work indicating that Müller glia in the adult retina possess stem cell character (see below).

Recently the role of Hes-5 in the mouse retina has been examined (Hojo et al. 2000) and has proven consistent with the role of Hes-1 described above. Misexpression of Hes-5 promoted Müller glial fate, and loss of Hes-5 function led to a reduced number of Müller glia. Although the *Hes* genes are currently the primary known effectors of Notch signaling, the effects of ActN in the retina were not completely recapitulated by expression of Hes-1 or Hes-5. Unlike ActN, these *Hes* genes did not promote enhanced proliferation among retinal progenitors, which suggests that Notch activation promoted proliferation through other *Hes* genes, or yet to be identified Notch targets.

Generally consistent with the frog and rodent studies, Scheer et al. (2001) have found that expression of ActN in the zebrafish retina can also promote Müller glial identity. This study used the Gal4/UAS system to drive ActN expression, and found that ActN-expressing cells had one of two fates, that of Müller glia or of seemingly undifferentiated cells. The authors also found that expression of ActN reduced proliferation of these cells, which is consistent with the frog data, but in contrast to the rodent data. One unique finding of the zebrafish study was the observation that the Müller glial marker zrf-1 was expressed three days early as a result of Notch activation. This premature expression suggested that rather than passively guiding retinal progenitors toward Müller glial fate, ActN actively promoted that fate. In contrast, in the rat study, no premature glial marker expression was observed. This difference may reflect variability between species, or a lack of sufficiently early Müller glial markers for use in the rat. All told, however, it seems clear from this body of work that Notch activation plays a central role during the generation of glia in the retina, although the extent to which this is an active role remains to be sorted out.

Radial Glia

Contemporary with the retinal work described above were gain-of-function studies examining the role of Notch signaling in the mouse telencephalon (Chambers et al. 2001, Gaiano et al. 2000, Ishibashi et al. 1994). The first such efforts used a retroviral vector to drive expression of Hes-1 in the embryonic neocortex (Ishibashi et al. 1994). This study found that while most control infected cells migrated away from the proliferative ventricular zone (VZ), cells expressing Hes-1 did not. Instead those cells remained in the VZ and later were detected in the adult ependymal layer,

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

an epithelial-like sheet of cells that lines the lateral ventricles and is considered the last vestige of the VZ. Although the ependymal fate of these cells was of limited interest at the time, it has become intriguing in light of more recent work suggesting that the ependyma may contain neural stem cells in the adult brain (see below). One unfortunate limitation of this study was the use of nuclear localized lacZ as the reporter, which prevented the authors from using morphology to identify cell type.

In a more recent study, our group examined the effects of ActN in the embryonic telencephalon (Gaiano et al. 2000). This study used retroviral vectors and the human placental alkaline phosphatase gene as the reporter to better visualize the morphology of infected cells. ActN was introduced into telencephalic progenitors in vivo at embryonic day (E)9.5 (prior to the onset of neurogenesis in this region) and was found to promote radial glial morphology and marker expression. Radial glia have their cell bodies in the VZ and extend a long radial process to the pial surface (Schmechel & Rakic 1979b). These cells have traditionally been thought to provide a migratory scaffold along which newly generated neurons migrate from the VZ to postmitotic areas (Rakic 1988, 1995). Thus, it seems plausible that these migratory neurons, expressing Notch ligands such as Delta, promote radial glial identity through the activation of Notch expressed along radial glial fibers (Figure 2). The recent observation that Delta-expressing cells are closely associated with radial glia supports this model (Campos et al. 2001). The promotion of radial glial identity by Notch activation suggests that the Hes-1 misexpression described above (Ishibashi et al. 1994) might also have promoted radial glial identity. While this may be true, it should not be assumed since ActN and Hes-1 do not have identical phenotypes in the rodent retina.

At first glance, the promotion of radial glial identity by ActN supports an instructive role for Notch in gliogenesis. Radial glia are one of the first cell types evident in the forebrain and as such are unlikely to represent a default state resulting from inhibition of all others cell types. Furthermore, ActN-infected cells were found to express the radial glial marker, brain lipid binding protein (BLBP), earlier and at higher levels than uninfected radial glia (Gaiano et al. 2000). This result is similar to the premature expression of zrf-1 observed in zebrafish retinal cells expressing ActN described above (Scheer et al. 2001). Such marker upregulation strongly suggests that Notch is actively promoting glial fate, rather than simply inhibiting other fates and indirectly leading to glial identity. Recent work examining the role of Notch in the cerebellum has suggested that Notch activation can promote Bergmann glial identity (R. Machold, D. Kittell, N. Gaiano, G. Fishell, in preparation). This result is not entirely surprising in that Bergmann glia are akin to the radial glia in the telencephalon, although Bergmann glia persist into adulthood.

When ActN-infected embryos were allowed to develop to adulthood, infected cells became astrocytes (Chambers et al. 2001, Gaiano et al. 2000), which is consistent with a known fate of radial glia (Schmechel & Rakic 1979b, Voigt 1989), and to a more limited extent ependymal cells. Interestingly, many infected cells were subependymal astrocytes, a cell type that in addition to ependymal cells

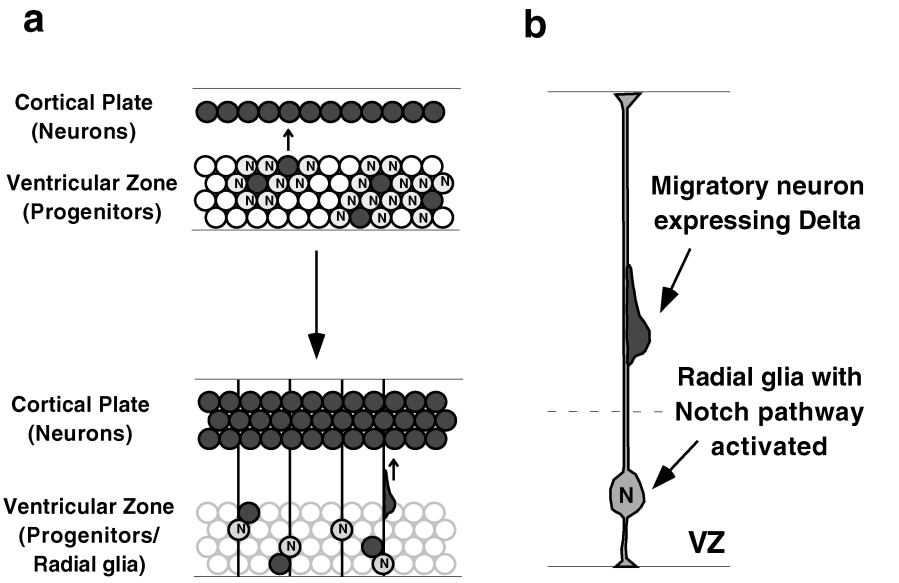

Figure 2 Model for generation and maintenance of radial glial identity during mouse brain development. (*a*) *Top*, some cells in the ventricular zone (VZ) express high levels of a Notch ligand, such as Delta (*dark gray*), as they prepare to leave the VZ. *Bottom*, adjacent cells have Notch activated in them (*light gray* with "N"), and attain radial glia morphology as development proceeds. (*b*) As Delta-expressing cells migrate out of the VZ to differentiate, they activate Notch in radial glia, thereby maintaining the radial glial scaffold (see Campos et al. 2001, Gaiano et al. 2000).

has been argued to possess stem cell character in the adult brain (Doetsch et al. 1999, Johansson et al. 1999, Laywell et al. 2000).

The promotion of radial glial identity by ActN embryonically, and of putative stem cell identity postnatally, suggests that radial glia may be the lineal precursors of adult neural stem cells. The idea that radial glia might be embryonic neural progenitors was proposed years ago (Alvarez-Buylla et al. 1990, Gray & Sanes 1992, Lendahl et al. 1990) and has recently gained substantial credence (see below). Consequently, the observation that Notch promotes radial glial identity may support, rather than contradict, the more traditional view that Notch promotes a progenitor state. Even so, the upregulation of BLBP indicates that the progenitor state promoted by Notch is likely to differ from that of the neuroepithelium as a whole.

Astrocytes

Our recent in vivo studies have found that, subsequent to promoting radial glial identity in the embryo, activation of Notch promoted astrocytic fate in the adult brain (Chambers et al. 2001, Gaiano et al. 2000). Although this in vivo work did not

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

address whether Notch acted instructively to specify astrocyte identity, a recent in vitro study has suggested that Notch can "instructively restrict" CNS stem cells to become astrocytes (Tanigaki et al. 2001). This latter work used adult hippocampal progenitors (AHPs), which are neural stem cells derived from the rat hippocampus. Using either stable transfection or retroviral infection, the authors introduced activated forms of Notch1 and Notch3 into AHPs. Consequently, they found that astrocyte identity was promoted at the expense of neuronal and oligodendroglial identity. The authors then determined whether transient activation of Notch1 was sufficient to promote astrocyte fate. They fused ActN1 to the estrogen receptor to create a form that would be nuclear localized (and thereby active) only in the presence of 4-hydroxytamoxifen. Transient activation (36 h) of this form of ActN1 was found to bias AHPs toward astrocyte identity as assayed four days later. The authors then showed that Notch's ability to generate astrocytes appears to be independent of the astrocyte inducing properties of ciliary neurotrophic factor (CNTF) (Bonni et al. 1997, Johe et al. 1996).

This study clearly suggested that Notch can instructively promote astrocyte fate. However, the evidence that it restricts progenitors to this fate should be qualified. Specifically, in a clonal analysis of AHPs continuously expressing ActN1 or ActN3, the authors found 20% of the clones to be purely neuronal and 40%–50% to be mixed (possessing neurons and astrocytes) (Tanigaki et al. 2001). Although this experiment did find enhanced astrogliogenesis in ActN-infected clones, the presence of so many neurons in these clones was not consistent with Notch activation restricting cells to an astrocytic fate. Nevertheless, the observation that Notch biases AHPs toward astrocytic fate is clearly of interest, in particular to those trying to control the fate of neural stem cells in vitro.

Oligodendrocytes

Although Notch can promote Müller glial, radial glial, and astroglial fates in the mammalian brain, Wang et al. (1998) have found that Notch activation inhibits oligodendroglial differentiation. In particular, this study examined the development of oligodendrocytes in the rat optic nerve. Prior to myelination of retinal ganglion cell axons, the optic nerve contains oligodendrocyte precursor cells (OPCs). Although in vivo these cells are likely to give rise exclusively to oligodendrocytes, they have been found in vitro to be capable of generating astrocytes (Raff et al. 1983) and even neurons (Kondo & Raff 2000). The study by Wang et al. (1998) showed that OPCs express Notch1, and that the Notch ligand Jagged1 is expressed by retinal ganglion cells along their axons. Furthermore, Jagged1 expression was found to be downregulated coincident with the initiation of retinal ganglion cell activity and myelination. These data suggest a model of optic nerve development in which retinal ganglion axons use Notch signaling to delay myelination until they innervate their targets (Figure 3). In support of this model, the study further showed that Notch activation in vitro could inhibit the differentiation of OPCs. In a subsequent study, the authors found that the helix loop helix transcriptional

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

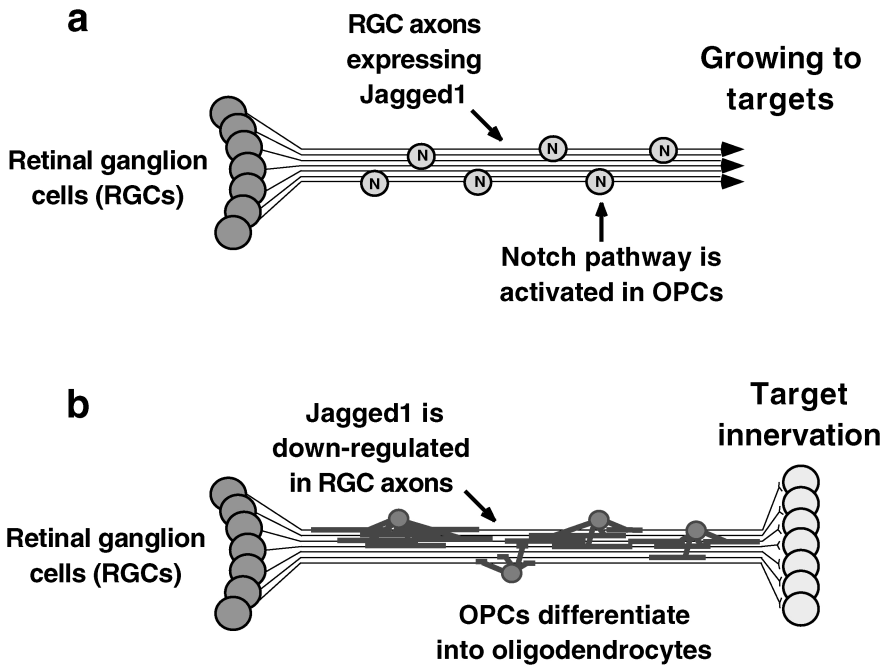

Figure 3 Model for optic nerve myelination as controlled by Notch-mediated inhibition of oligodendrocyte differentiation. (*a*) While retinal ganglion cells (RGCs) are growing to targets, their axons express the Notch ligand Jagged1. In the process they inhibit oligodendrocyte precursor cells (OPCs) from differentiating into oligodendrocytes and initiating myelinating. (*b*) After target innervation Jagged1 is downregulated in RGC axons and the OPCs proceed to differentiate (see Wang et al. 1998). The observations that Notch can promote Müller glial, radial glial, and astroglial fates in the mammalian CNS while inhibiting oligodendroglial differentiation suggests that the role of Notch during mammalian gliogenesis is not uniform. However, it is worth noting that oligodendrocytes are functionally unique among the CNS macroglia, and there is no reason to expect that Notch or any signaling pathway should behave similarly in such diverse cell types simply because they fall into the same broad class.

repressor Id2 can also inhibit OPC differentiation (Wang et al. 2001), although the role of Notch in this inhibition remains to be clarified.

Schwann Cells

In the mammalian PNS the neural crest is a multipotent precursor population that gives rise to a wide variety of cell types including neurons and Schwann cells. Functionally, Schwann cells are the PNS equivalent of oligodendrocytes in that they myelinate peripheral axons. However, unlike the inhibitory role Notch appears to play during oligodendrocyte development (see above), a recent study has

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

suggested that Notch irreversibly commits neural crest stem cells (NCSCs) to Schwann cell fate (Morrison et al. 2000). Initially, the authors found that expression of activated Notch in NCSCs in vivo inhibited neuronal differentiation. To examine the effect of activated Notch in the neural crest in vitro, the authors isolated NCSCs from the E14.5 rat sciatic nerve, and consistent with the in vivo data, neuronal differentiation was inhibited. In addition, the study found that both the rate and extent of Schwann cell differentiation was increased even after transient Notch activation. This result supported an instructive role for Notch in promoting Schwann cell fate. Furthermore, when transient Notch activation in NCSCs was followed by exposure to bone morphogenetic protein 2, a cue that promotes neuronal fate, the cells still became Schwann cells. Thus, transient Notch activation appeared not only to have instructed NCSCs toward Schwann cell fate, but to have done so irreversibly.

In an interesting twist, when Notch activation was performed coincident with exposure to bone morphogenetic protein 2, both Schwann cell and myofibroblast fate (a third cell type that can be derived from NCSCs in vitro) were promoted at the expense of neurons. This result showed that the influence of Notch could be modified by additional signals, underscoring the notion that even this seemingly instructive role of Notch is context dependent. Subsequent work has found that the response of NCSCs to Notch activation varies considerably depending on the age and location from which the cells are derived, further demonstrating the importance of the cellular "ground" state (S.J. Morrison, personal communication).

There are clear parallels between the studies of Notch's role in oligodendrocyte and Schwann cell development that make the contrasting outcomes challenging to understand. In both cases the precursor cells, rather than being derived from nascent progenitor pools, were derived from developing nerve tracts (OPCs from the optic nerve, and NCSCs from the sciatic nerve) (Morrison et al. 2000, Wang et al. 1998). Both the OPCs and NCSCs used in these studies have been found to be multipotent in vitro, although they are likely to give rise primarily to their respective myelinating cell types in vivo. Why then does Notch appear to have the opposite effect on these precursor populations? The simple answer may be that regardless of their similarities, OPCs and NCSCs are nonetheless different cell types, with distinct origins and intrinsic characters. The ability of Notch to promote gliogenesis in one cell type, while blocking it in a similar cell type, supports the premise that an instructive role for Notch in gliogenesis cannot be assigned without contextual consideration.

NOTCH, GLIA, AND STEM CELLS?

In vertebrates, the traditional view has been that Notch signaling inhibits differentiation and maintains cells as progenitors. In contrast, the newly emerging view is that Notch can positively promote certain glial fates, and as such may serve as an instructive signal. The maintenance of a progenitor state and the promotion of glial identity may seem mutually exclusive, however, recent studies examining the

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

developmental potential of "differentiated" glia have suggested that some glial cell types can possess progenitor character (Doetsch et al. 1999, Fischer & Reh 2001, Laywell et al. 2000).

Several recent reports have found that radial glia may be multipotent neural progenitors in the embryo (Hartfuss et al. 2001, Malatesta et al. 2000, Noctor et al. 2001). One such study examined the potential of isolated cortical radial glia in vitro and found that in addition to generating glial daughters, these cells can also gave rise to neurons (Malatesta et al. 2000). Noctor et al. (2001) provided further evidence that radial glia can generate neurons using time-lapse video observation of single-labeled radial glia in slice culture. The authors observed radial glia dividing and producing daughter cells that migrated to the cortical plate and expressed neuronal markers. In light of these data, the promotion of radial glial identity by ActN suggests that Notch may promote progenitor fate (Gaiano et al. 2000). Furthermore, recent analysis suggests that cells infected with ActN in vivo can display multipotent stem cell character when placed in vitro (N. Gaiano, S. Nery, M. Rutlin, F. Radtke, & G. Fishell, submitted). Whether all radial glia specified by Notch have stem cell character is unknown. Götz and colleagues have suggested that some radial glia are neurogenic, some are gliogenic, and others are multipotent (Malatesta et al. 2000). If at least some radial glia are embryonic neural stem cells, they are likely to be lineally related to stem cells present in the adult brain (see Figure 4). In the past, the observation that the radial glia scaffold transformed into astrocytes postnatally (Schmechel & Rakic 1979b, Voigt 1989) suggested that radial glia were committed glial cells that maintained a specialized morphology during development (Levitt et al. 1981, 1983; Schmechel & Rakic 1979a). More recently, however, several groups have suggested that astrocytes are capable of generating neurons and may be neural stem cells in the adult brain (Doetsch et al. 1999, Laywell et al. 2000). This work, together with the observation that Notch can promote astrocyte identity, support the notion that in addition to specifying glial fate, Notch may be maintaining stem cell character. Further support for this idea has come from recent evidence that Müller glia, which are specified at least in part by Notch, may be multipotent stem cells in the adult retina. Fischer & Reh (2001) have found in the chick that subsequent to retinal damage, Müller glia can re-enter the cell cycle and give rise to new retinal neurons as well as additional Müller glia.

The idea that mature cell types, such as astrocytes and Müller glia, are stem cells may seem at odds with the traditional view that stem cells do not express markers of differentiated cell types. However, recent studies in a variety of tissues, including the nervous system, have suggested that this traditional view was misleading (Fuchs & Segre 2000). In the skin, for example, stem cells have been found to express markers previously thought to be present only in differentiated keratinocytes. Similarly, it has recently been suggested that both intestinal and hematopoietic stem cells possess molecular and/or morphological characteristics of differentiated cell types (Fuchs & Segre 2000).

While it is becoming increasingly believable that some glia may be stem cells in the adult vertebrate nervous system, there is certainly no reason to think that

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

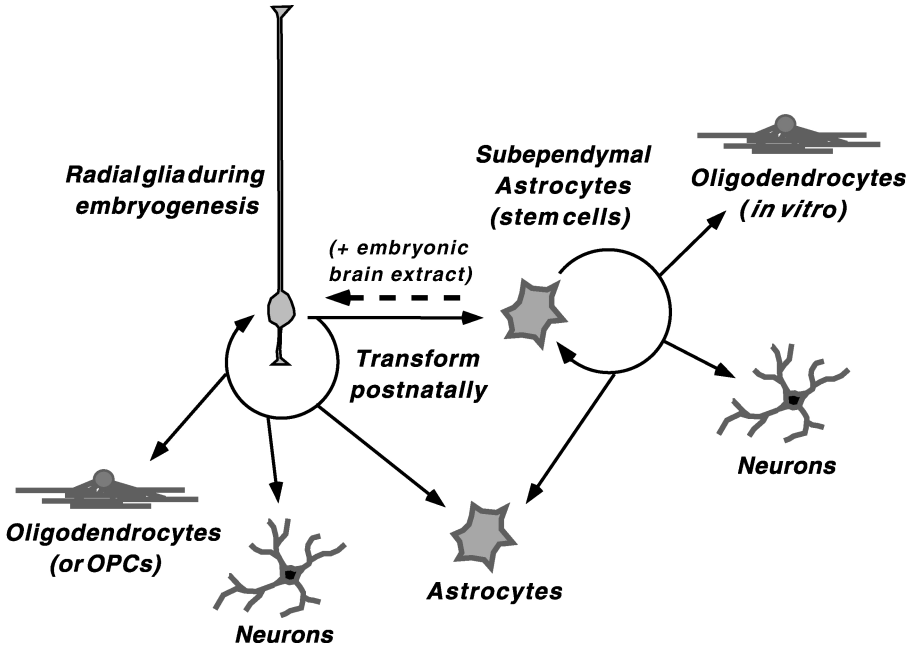

Figure 4 Model of radial glia and astrocytes as lineally related multipotent progenitors. During embryogenesis radial glia can give rise to both neurons and glia. As radial glia transform into astrocytes postnatally, some retain stem cell character in the form of specialized astrocytes present in the subependymal layer. These cells have been found to be capable of self-renewal as well as the generation of all three major CNS cell types in vitro (see Doetsch et al. 1999). When exposed to embryonic cues, astrocytes may reacquire an embryonic progenitor state (see Hunter & Hatten 1995), which suggests a reversible continuum between these cell types.

all glia are stem cells. Prior to any suspicions about their stem cell character, glia were known to play many fundamental supporting roles in the functioning of the mature nervous system. Even among those glial cell types recently suggested to possess stem cell character, only subsets are likely to be stem cells. For example, while both subependymal and dispersed astrocytes have been found to possess stem cell character early postnatally, dispersed astrocytes gradually lose this stem cell character (Laywell et al. 2000).

So what is the relationship between Notch, glia, and stem cells? The observations that Notch can induce early expression of glial markers in certain neural progenitors suggest that it is altering these cells. For example, the expression of BLBP in radial glia specified by ActN clearly distinguishes these cells from neuroepithelial progenitors present early in development (Gaiano et al. 2000). One possibility is that BLBP-expressing radial glia represent a more "mature" progenitor

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

state, which is precociously promoted by expression of ActN. These cells may be the embryonic form of astrocytic stem cells present in the adult. The only difference between these cells might be their environment; the promotion of radial glial and astrocytic fates by ActN is the same phenomenon at different times. This notion is supported by the observation that astrocytes revert into radial glia in the presence of embryonic brain extract (Hunter & Hatten 1995) (see Figure 4). Interestingly, in primates radial glia express the canonical astrocytic marker, glial fibrillary acidic protein, during development (Levitt & Rakic 1980). The relationship between radial glia and astrocytes, with regard to their potential stem cell properties, has recently been discussed by Alvarez-Buylla and colleagues (2001).

On a final note, of the four glial cell types recently found to be specified by Notch, three have also been found to possess potential stem cell character: radial glia, astrocytes, and Müller glia. This begs the question, do the Schwann cells induced by Notch in NCSCs also possess such character? The studies by Morrison et al. (2000) suggest that this is unlikely. However, as the impact of Notch in NCSCs can vary depending on age and environment (S.J. Morrison, personal communication), perhaps under the right circumstances the Schwann cells specified by Notch activation might exhibit stem cell character as well. Supporting this notion, a recent study has shown that, in certain conditions, OPCs can be transformed into neural stem cells in vitro (Kondo & Raff 2000). Interestingly, like radial glia (in primates), Müller glia (in the context of retinal damage), and astrocytes, Schwann cells derived from NCSCs also express glial fibrillary acidic protein (Shah et al. 1994, Stemple & Anderson 1992), which suggests a commonality between these cell types.

CONCLUSIONS

In the past, Notch signaling has not been considered instructive because it was believed to have a nonspecific inhibitory effect on cellular differentiation. As such the Notch pathway was thought to passively influence cell fate by controlling the ability of progenitors to respond to instructive developmental cues. However, the recent data discussed in this review has suggested that Notch can play a more active role in directing cell fate. Specifically, many studies have found evidence of a role for Notch in promoting glial and perhaps stem cell identities. While intriguing, it is worth noting that this role is context dependent, both in vertebrates and in invertebrates, as Notch can either promote or inhibit gliogenesis, depending on the cell type being examined. Therefore, although in specific contexts the role of Notch might be termed instructive, it is currently not possible to define a uniform role for Notch with regard to glial fate.

The flurry of recent studies regarding the influence of Notch during gliogenesis has significantly altered our understanding of the role of this pathway during development. Further study promises to clarify the relationships between Notch signaling, gliogenesis, and the maintenance of stem cell populations both in the embryo and the adult. Particularly important will be identifying the molecular targets of the Notch pathway, as well as the manner in which Notch signaling interacts

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

with other signaling pathways that influence cell fate. By better understanding the molecular circuitry downsteam of Notch, we will gain fundamental insight into the global regulation not only of glial specification, but also the maintenance of progenitor identity.

ACKNOWLEDGMENTS

The authors are grateful to members of the Fishell Lab and the Developmental Genetics Program at the Skirball Institute for continuous intellectual input. The authors have been funded by a postdoctoral fellowship from the American Cancer Society (PF4473 to N. G.), a Career Development Award from the Burroughs Wellcome Fund (to N. G.), a grant from the Children's Brain Tumor Foundation (to G. F.), and a grant from the NINDS (NS32993 to G. F.).

LITERATURE CITED

Alvarez-Buylla A, Theelen M, Nottebohm F. 1990. Proliferation "hot spots" in adult avian ventricular zone reveal radial cell division. *Neuron* 5:101–9

Anderson AC, Robey EA, Huang YH. 2001. Notch signaling in lymphocyte development. *Curr. Opin. Genet. Dev.* 11:554–60

Artavanis-Tsakonas S, Delidakis C, Fehon RG. 1991. The Notch locus and the cell biology of neuroblast segregation. *Annu. Rev. Cell Biol.* 7:427–52

Artavanis-Tsakonas S, Rand MD, Lake RJ. 1999. Notch signaling: cell fate control and signal integration in development. *Science* 284:770–76

Bao ZZ, Cepko CL. 1997. The expression and function of Notch pathway genes in the developing rat eye. *J. Neurosci.* 17:1425–34

Barrantes IB, Elia AJ, Wunsch K, De Angelis MH, Mak TW, et al. 1999. Interaction between Notch signalling and Lunatic fringe during somite boundary formation in the mouse. *Curr. Biol.* 9:470–80

Bhat KM. 1999. Segment polarity genes in neuroblast formation and identity specification during Drosophila neurogenesis. *Bioessays* 21:472–85

Bonni A, Sun Y, Nadal-Vicens M, Bhatt A, Frank DA, et al. 1997. Regulation of gliogenesis in the central nervous system by the JAK-STAT signaling pathway. *Science* 278:477–83

Campos LS, Duarte AJ, Branco T, Henrique D. 2001. mDll1 and mDll3 expression in the developing mouse brain: role in the establishment of the early cortex. *J. Neurosci. Res.* 64:590–98

Campos-Ortega JA. 1993. Mechanisms of early neurogenesis in Drosophila melanogaster. *J. Neurobiol.* 24:1305–27

Chambers CB, Peng Y, Nguyen H, Gaiano N, Fishell G, Nye JS. 2001. Spatiotemporal selectivity of response to Notch1 signals in mammalian forebrain precursors. *Development* 128:689–702

Coffman CR, Skoglund P, Harris WA, Kintner CR. 1993. Expression of an extracellular deletion of Xotch diverts cell fate in Xenopus embryos. *Cell* 73:659–71

Doe CQ, Skeath JB. 1996. Neurogenesis in the insect central nervous system. *Curr. Opin. Neurobiol.* 6:18–24

Doetsch F, Caille I, Lim DA, Garcia-Verdugo JM, Alvarez-Buylla A. 1999. Subventricular zone astrocytes are neural stem cells in the adult mammalian brain. *Cell* 97:703–16

Dorsky RI, Rapaport DH, Harris WA. 1995. Xotch inhibits cell differentiation in the Xenopus retina. *Neuron* 14:487–96

Fischer AJ, Reh TA. 2001. Muller glia are a potential source of neural regeneration in the postnatal chicken retina. *Nat. Neurosci.* 4: 247–52

Fuchs E, Segre JA. 2000. Stem cells: a new lease on life. *Cell* 100:143–55

Furukawa T, Maruyama S, Kawaichi M, Honjo T. 1992. The Drosophila homolog of the immunoglobulin recombination signal-binding protein regulates peripheral nervous system development. *Cell* 69:1191–97

Furukawa T, Mukherjee S, Bao ZZ, Morrow EM, Cepko CL. 2000. rax, Hes1, and notch1 promote the formation of Muller glia by postnatal retinal progenitor cells. *Neuron* 26:383–94

Gaiano N, Nye JS, Fishell G. 2000. Radial glial identity is promoted by Notch1 signaling in the murine forebrain. *Neuron* 26:395–404

Gho M, Bellaiche Y, Schweisguth F. 1999. Revisiting the Drosophila microchaete lineage: a novel intrinsically asymmetric cell division generates a glial cell. *Development* 126:3573–84

Gray GE, Sanes JR. 1992. Lineage of radial glia in the chicken optic tectum. *Development* 114:271–83

Guo M, Jan LY, Jan YN. 1996. Control of daughter cell fates during asymmetric division: interaction of Numb and Notch. *Neuron* 17:27–41

Hartenstein AY, Rugendorff A, Tepass U, Hartenstein V. 1992. The function of the neurogenic genes during epithelial development in the Drosophila embryo. *Development* 116: 1203–20

Hartfuss E, Galli R, Heins N, Gotz M. 2001. Characterization of CNS precursor subtypes and radial glia. *Dev. Biol.* 229:15–30

Hojo M, Ohtsuka T, Hashimoto N, Gradwohl G, Guillemot F, Kageyama R. 2000. Glial cell fate specification modulated by the bHLH gene Hes5 in mouse retina. *Development* 127:2515–22

Hosoya T, Takizawa K, Nitta K, Hotta Y. 1995. Glial cells missing: a binary switch between neuronal and glial determination in Drosophila. *Cell* 82:1025–36

Hunter KE, Hatten ME. 1995. Radial glial cell transformation to astrocytes is bidirectional: regulation by a diffusible factor in embryonic forebrain. *Proc. Natl. Acad. Sci. USA* 92:2061–65

Irvine KD, Vogt TF. 1997. Dorsal-ventral signaling in limb development. *Curr. Opin. Cell. Biol.* 9:867–76

Ishibashi M, Moriyoshi K, Sasai Y, Shiota K, Nakanishi S, Kageyama R. 1994. Persistent expression of helix-loop-helix factor HES-1 prevents mammalian neural differentiation in the central nervous system. *Embo. J.* 13: 1799–1805

Jacobs JR, Hiromi Y, Patel NH, Goodman CS. 1989. Lineage, migration, and morphogenesis of longitudinal glia in the Drosophila CNS as revealed by a molecular lineage marker. *Neuron* 2:1625–31

Jan YN, Jan LY. 1994. Genetic control of cell fate specification in Drosophila peripheral nervous system. *Annu. Rev. Genet.* 28:373–93

Jiang YJ, Aerne BL, Smithers L, Haddon C, Ish-Horowicz D, Lewis J. 2000. Notch signalling and the synchronization of the somite segmentation clock. *Nature* 408:475–79

Johansson CB, Momma S, Clarke DL, Risling M, Lendahl U, Frisen J. 1999. Identification of a neural stem cell in the adult mammalian central nervous system. *Cell* 96:25–34

Johe KK, Hazel TG, Muller T, Dugich-Djordjevic MM, McKay RD. 1996. Single factors direct the differentiation of stem cells from the fetal and adult central nervous system. *Genes. Dev.* 10:3129–40

Jones BW, Fetter RD, Tear G, Goodman CS. 1995. Glial cells missing: a genetic switch that controls glial versus neuronal fate. *Cell* 82:1013–23

Knust E, Campos-Ortega JA. 1989. The molecular genetics of early neurogenesis in Drosophila melanogaster. *Bioessays* 11:95–100

Kondo T, Raff M. 2000. Oligodendrocyte precursor cells reprogrammed to become

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

multipotential CNS stem cells. *Science* 289: 1754–57

Laywell ED, Rakic P, Kukekov VG, Holland EC, Steindler DA. 2000. Identification of a multipotent astrocytic stem cell in the immature and adult mouse brain. *Proc. Natl. Acad. Sci. USA* 97:13,883–88

Lendahl U, Zimmerman LB, McKay RD. 1990. CNS stem cells express a new class of intermediate filament protein. *Cell* 60:585–95

Levitt P, Cooper ML, Rakic P. 1981. Coexistence of neuronal and glial precursor cells in the cerebral ventricular zone of the fetal monkey: an ultrastructural immunoperoxidase analysis. *J. Neurosci.* 1:27–39

Levitt P, Cooper ML, Rakic P. 1983. Early divergence and changing proportions of neuronal and glial precursor cells in the primate cerebral ventricular zone. *Dev. Biol.* 96:472–84

Levitt P, Rakic P. 1980. Immunoperoxidase localization of glial fibrillary acidic protein in radial glial cells and astrocytes of the developing rhesus monkey brain. *J. Comp. Neurol.* 193:815–40

Lewis J. 1996. Neurogenic genes and vertebrate neurogenesis. *Curr. Opin. Neurobiol.* 6:3–10

Lewis J. 1998. Notch signalling and the control of cell fate choices in vertebrates. *Semin. Cell. Dev. Biol.* 9:583–89

Malatesta P, Hartfuss E, Gotz M. 2000. Isolation of radial glial cells by fluorescent-activated cell sorting reveals a neuronal lineage. *Development* 127:5253–63

Modolell J. 1997. Patterning of the adult peripheral nervous system of Drosophila. *Perspect. Dev. Neurobiol.* 4:285–96

Morrison SJ, Perez SE, Qiao Z, Verdi JM, Hicks C, et al. 2000. Transient Notch activation initiates an irreversible switch from neurogenesis to gliogenesis by neural crest stem cells. *Cell* 101:499–510

Mumm JS, Kopan R. 2000. Notch signaling: from the outside in. *Dev. Biol.* 228:151–65

Nieto M, Schuurmans C, Britz O, Guillemot F. 2001. Neural bHLH genes control the neuronal versus glial fate decision in cortical progenitors. *Neuron* 29:401–13

Noctor SC, Flint AC, Weissman TA, Dammerman RS, Kriegstein AR. 2001. Neurons derived from radial glial cells establish radial units in neocortex. *Nature* 409:714–20

Nye JS, Kopan R, Axel R. 1994. An activated Notch suppresses neurogenesis and myogenesis but not gliogenesis in mammalian cells. *Development* 120:2421–30

Osborne B, Miele L. 1999. Notch and the immune system. *Immunity* 11:653–63

Raff MC, Miller RH, Noble M. 1983. A glial progenitor cell that develops in vitro into an astrocyte or an oligodendrocyte depending on culture medium. *Nature* 303:390–96

Rakic P. 1988. Specification of cerebral cortical areas. *Science* 241:170–76

Rakic P. 1995. Radial versus tangential migration of neuronal clones in the developing cerebral cortex. *Proc. Natl. Acad. Sci. USA* 92:11,323–27

Reddy GV, Rodrigues V. 1999. A glial cell arises from an additional division within the mechanosensory lineage during development of the microchaete on the Drosophila notum. *Development* 126:4617–22

Scheer N, Groth A, Hans S, Campos-Ortega JA. 2001. An instructive function for Notch in promoting gliogenesis in the zebrafish retina. *Development* 128:1099–107

Schmechel DE, Rakic P. 1979a. Arrested proliferation of radial glial cells during midgestation in rhesus monkey. *Nature* 277:303–5

Schmechel DE, Rakic P. 1979b. A Golgi study of radial glial cells in developing monkey telencephalon: morphogenesis and transformation into astrocytes. *Anat. Embryol.* (*Berl.*) 156:115–52

Schweisguth F. 1995. Suppressor of Hairless is required for signal reception during lateral inhibition in the Drosophila pupal notum. *Development* 121:1875–84

Schweisguth F, Posakony JW. 1992. Suppressor of Hairless, the Drosophila homolog of the mouse recombination signal-binding protein gene, controls sensory organ cell fates. *Cell* 69:1199–212

Seydoux G, Greenwald I. 1989. Cell autonomy of lin-12 function in a cell fate decision in C. elegans. *Cell* 57:1237–45

22 Mar 2002 12:23 AR AR160-15.tex AR160-15.sgm LaTeX2e(2002/01/18) P1: GJB
AR REVIEWS IN ADVANCE10.1146/annurev.neuro.25.030702.130823

Shah NM, Marchionni MA, Isaacs I, Stroobant P, Anderson DJ. 1994. Glial growth factor restricts mammalian neural crest stem cells to a glial fate. *Cell* 77:349–60

Skeath JB, Doe CQ. 1996. The achaete-scute complex proneural genes contribute to neural precursor specification in the Drosophila CNS. *Curr. Biol.* 6:1146–52

Stemple DL, Anderson DJ. 1992. Isolation of a stem cell for neurons and glia from the mammalian neural crest. *Cell* 71:973–85

Sternberg PW, Horvitz HR. 1989. The combined action of two intercellular signaling pathways specifies three cell fates during vulval induction in C. elegans. *Cell* 58:679–93

Sun Y, Nadal-Vicens M, Misono S, Lin MZ, Zubiaga A, et al. 2001. Neurogenin promotes neurogenesis and inhibits glial differentiation by independent mechanisms. *Cell* 104:365–76

Tanigaki K, Nogaki F, Takahashi J, Tashiro K, Kurooka H, Honjo T. 2001. Notch1 and Notch3 instructively restrict bFGF-responsive multipotent neural progenitor cells to an astroglial fate. *Neuron* 29:45–55

Udolph G, Rath P, Chia W. 2001. A requirement for Notch in the genesis of a subset of glial cells in the Drosophila embryonic central nervous system which arise through asymmetric divisions. *Development* 128:1457–66

Van De Bor V, Giangrande A. 2001. Notch signaling represses the glial fate in fly PNS. *Development* 128:1381–90

Van De Bor V, Walther R, Giangrande A. 2000. Some fly sensory organs are gliogenic and require glide/gcm in a precursor that divides symmetrically and produces glial cells. *Development* 127:3735–43

Vargesson N, Patel K, Lewis J, Tickle C. 1998. Expression patterns of Notch1, Serrate1, Serrate2 and Delta1 in tissues of the developing chick limb. *Mech. Dev.* 77:197–99

Vincent S, Vonesch JL, Giangrande A. 1996. Glide directs glial fate commitment and cell fate switch between neurones and glia. *Development* 122:131–39

Voigt T. 1989. Development of glial cells in the cerebral wall of ferrets: direct tracing of their transformation from radial glia into astrocytes. *J. Comp. Neurol.* 289:74–88

Wang S, Sdrulla A, Johnson JE, Yokota Y, Barres BA. 2001. A role for the helix-loop-helix protein Id2 in the control of oligodendrocyte development. *Neuron* 29:603–14

Wang S, Sdrulla AD, diSibio G, Bush G, Nofziger D, et al. 1998. Notch receptor activation inhibits oligodendrocyte differentiation. *Neuron* 21:63–75

Weinmaster G. 1997. The ins and outs of notch signaling. *Mol. Cell. Neurosci.* 9:91–102

Xu T, Rebay I, Fleming RJ, Scottgale TN, Artavanis-Tsakonas S. 1990. The Notch locus and the genetic circuitry involved in early Drosophila neurogenesis. *Genes. Dev.* 4:464–75