Comment

Precursor Cell Transitions in Oligodendrocyte Development

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The physiological demands made upon precursor cell populations during different developmental epochs can be remarkably divergent, particularly in tissues that do not undergo constant turnover in the adult animal. In such tissues, with the central nervous system (CNS) being a prime example, the rapid increase in numbers of precursor cells and their differentiated progeny becomes turned off over a relatively short period of time. Once this period of rapid cell generation ends, precursor cell populations may be maintained in the adult tissue to participate in homeostatic cell replacement during normal function and to repair damaged tissue following injury. The regulation of the precursor cells resident in adult tissue must, however, be different in some manner from that which characterizes the explosive growth of early development.

It would be of great interest to understand the biological basis for the different behavior of precursor cell populations in developing and adult tissues, but there are very few cellular lineages that have been sufficiently well characterized to enable such studies. One of the few such lineages is the one that gives rise to oligodendrocytes, the myelin-forming cells of the CNS. Oligodendrocytes arise from a well-defined precursor cell that also can give rise to a specific astrocyte population (the type-2 astrocyte) in vitro (Raff et al., 1983), although, thus far, it appears that this astrocyte pathway is not used during development (Skoff, 1990). Due to this disparity, this single precursor cell is alternatively called an oligodendrocyte type-2 astrocyte (O-2A) progenitor or an oligodendrocyte precursor cell (OPC). O-2A/OPCs can be readily purified from animals of various ages, can be induced to expand and differentiate readily in vitro, and, in general, have provided an exceptional population in which to study developmental transitions. The report in this issue of *JCB* from Tang et al. (2000) is an excellent example of such a study.

The research that forms the basis for the studies of Tang et al. (2000) is based on the earlier observations that the developing CNS and the adult CNS both contain O-2A/OPCs (ffrench-Constant and Raff, 1986; Wolswijk and Noble, 1989), but these cells differ from each other in a number of important features (Table I). For example, O-2A/OPCs^{perinatal} divide rapidly (18 h), migrate rapidly (21 μm/h), and differentiate rapidly into oligodendrocytes when grown in serum-free medium in the absence of mitogens. O-2A/OPCs^{adult}, in contrast, divide, differentiate, and migrate much more slowly (Wolswijk and Noble, 1989; see Table I). In addition, O-2A/OPCs^{perinatal} can be induced by external signaling molecules to undergo a pattern of differentiation in which all members of a single clone turn into oligodendrocytes in a relatively synchronous and symmetric manner (Temple and Raff, 1986; Raff et al., 1988; Barres et al., 1994; Ibarrola et al., 1996). In contrast, in these same conditions, O-2A/OPCs^{adult} predominantly generate oligodendrocytes in association with asymmetric division and differentiation (Wren et al., 1992). These several differences appear to be cell intrinsic, in that *perinatal* and *adult* O-2A/OPCs seem to coexist in the optic nerve in vivo between 2 and 4 wk after birth, and express their characteristic phenotypes even when they are grown together in the same tissue culture dish (Wolswijk et al., 1990).

The existence of two O-2A/OPC populations with properties so distinct as those of the perinatal and adult CNS raises the question of what the developmental relationship between these two populations might be. In previous studies, it was shown, by time–lapse microcinematography, that O-2A/OPCs^{perinatal} isolated from optic nerves of 7-d-old rat pups can give rise directly to cells with the characteristics of O-2A/OPCs^{adult}, thus demonstrating a direct lineage relationship between these populations (Wren et al., 1992).

The present studies extend on previous investigations of the relationship between *perinatal* and *adult* O-2A/OPCs by studying the transition from the former population to the latter over a heroic 390-d observation period. Unlike previous studies, the research by Tang et al. (2000) was carried out using purified cultures of cells, so as to ask the question of whether the maturational changes these cells undergo is regulated by the environment or is the result of cell-intrinsic processes.

The data provided by Tang et al. (2000) demonstrate clearly that all of the information required to undergo the transition from a *perinatal* to an *adult* phenotype resides

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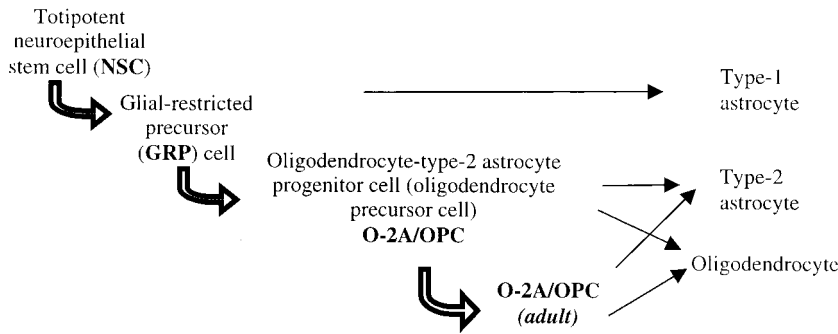
Table I. Key Distinguishing Characteristics of perinatal and adult O-2A/OPCs

	O-2A/OPC^{perinatal}	O-2A/OPC^{adult}
Cell cycle length	18 ± 4 h	65 ± 18 h
Migration rate	21.4 ± 1.6 μm/h	4.3 ± 0.7 μm/h
Time to differentiation of 50% of cells into oligodendrocytes in mitogen-free conditions	48	72–120

Figure 1. Diagrammatic view of the relationship between different precursor cells and differentiated cell types of the CNS in specific respect to oligodendrocyte generation. Curved arrows indicate the generation of a lineage-restricted precursor cell, while straight arrows indicate the currently understood derivation of a differentiated cell type.

within the O-2A/OPC itself. Purified cells derived from P7 rats, passaged in chemically defined medium supplemented with platelet-derived growth factor (PDGF, a potent mitogen for these cells; Noble et al., 1988; Raff et al., 1988; Richardson et al., 1988), showed a steady change in their phenotype, acquiring over time a longer cell cycle, a slower migration rate and a slower time course of differentiation. The data are interpreted in favor of the hypothesis that these changes are brought about by the playing out of a cell-intrinsic program of maturation. It might be argued that as the cultures studied actually contained multiple cells, some of which were oligodendrocytes rather than O-2A/OPCs, it is possible that secreted signaling molecules produced by the oligodendrocytes were relevant to this process. This argument cannot be dismissed, but what one can certainly say is that the ability to carry out this maturational program is an intrinsic property of the O-2A/OPC lineage.

One curious aspect of the present studies is that the transition from *perinatal* to *adult* O-2A/OPC phenotypes takes longer to occur than the period of time indicated in previous studies. In vivo, the first O-2A/OPCs with *adult*-like characteristics are found at 14 d after birth, and have almost completely replaced the *perinatal* population over the next two weeks (Wolswijk et al., 1990). Moreover, in mixed (astrocyte-containing) optic nerve cultures supplemented with thyroid hormone, some clones of P7-derived O-2A/OPCs can undergo what appears to be a relatively complete transition over the course of two divisions and several days in vitro (Wren et al., 1992). In contrast, in the passaging experiments of Tang et al. (2000) it appears that a complete transition might take as long as 300 d when O-2A/OPCs are grown in pure culture and not exposed to thyroid hormone. One possible explanation for such divergent time courses is that although there is a cell-intrinsic process that underlies this maturation, the time course over which it occurs can be hastened by particular cell-signaling molecules.

The type of developmental transition studied by Tang et al. (2000) differs significantly from the more widely studied transitions associated with restriction of differentiation potential within a sequential lineage of precursor cells. For example, it now appears that oligodendrocyte generation requires the initial generation of tripotential glial-restricted precursor (GRP) cells from totipotent neuroepithelial stem cells (Fig. 1; Rao and Mayer-Pröschel, 1997). These tripotential GRP cells then give rise to bipotential O-2A/OPCs, which appear thus far to be a necessary an-

cestor of oligodendrocytes themselves (Gregori et al., submitted). In contrast, the transition of O-2A/OPCs from a *perinatal* to an *adult* phenotype (Wren et al., 1992; Tang et al., 2000) is not associated with any further restrictions in differentiation potential.

Despite the lack of further lineage restriction in the transition from *perinatal* to *adult* O-2A/OPCs, one wonders whether all of the above transitions in this lineage are regulated by similar molecular switches, and one wonders what these switches might be. Certainly, the studies on maturation in the O-2A/OPC provide a very different view of cellular aging than is derived from studies on cellular senescence. As the O-2A/OPC[perinatal] goes through its continuing cell cycles, it does not appear to reach a stage where division is no longer possible. Instead, as shown previously (Gao and Raff, 1997), rapidly dividing cells from late embryos intrinsically mature into the less rapidly dividing cells of the postnatal animal, which themselves give rise to slowly dividing *adult* cells (Wren et al., 1992; Tang et al., 2000). Thus, the transition that occurs with continued division of O-2A/OPCs in vitro is very different from that which occurs in, e.g., dividing fibroblasts, which reach a point (termed senescence) at which they no longer divide at all. In contrast, aging in the O-2A/OPC lineage is associated instead with the emergence of a new population of precursor cells with fundamentally different properties, including a much increased cell cycle length. Such results give strong support to the view that maturational processes associated with aging of precursor cells include biological alterations that may prove far more subtle than, e.g., telomere shortening. In addition, it would be of interest to know whether the maturational transition that has now been so well described in the O-2A/OPC lineage represents a general model by which the lineage-restricted long-lived stem cells of the adult animal are generated during the process of early development.

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