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Review Article

# Cellular Changes in Neuroepithelium During Neurogenesis and Gliogenesis

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## Abstract

The nervous system is derived from the ectodermal germ layer which is one of the three main germ layers of the embryo. A series of fascinating highly regulated, still highly complex molecular, cellular, and morphological changes beginning in the early embryonic period occur within the neuroepithelium. The neuroepithelium of the neural plate which is simple columnar epithelium at the beginning but pseudostratified columnar epithelium during cellular differentiation gives rise to the neurons and glial cells except for the microglia cells. Neural stem/progenitor cells expand as neuroepithelial cells by symmetric proliferative divisions and then at the onset of neurogenesis transform into radial glial cells after switching to asymmetric neurogenic divisions. The radial glial cells generate directly or indirectly all neurons and glial cells. In this mini-review, I tried to summarize the transformation of the neuroectoderm into a neural tube, the main stem/progenitor cells of the neuroepithelium, symmetrical and asymmetrical division, differentiation, and migration patterns of the neuroepithelial cells.

***Keywords:*** *Neuroepithelium; Neurogenesis; Gliogenesis; Radial Glial Cells*

## Introduction

The nervous system derived from the ectodermal germ layer is the success of a fascinating series of highly regulated, still highly complex molecular, cellular, and morphological changes beginning in the early embryonic period. At the beginning of 3rd week, the ectoderm called the neural plate is a disk-shaped area where the cephalic end is larger than the caudal end (Figure 1) [1]. During the early development of the vertebrate embryo, neural fate is induced in the ectoderm by the underlying notochord [2]. The neuroepithelium of the neural plate which is simple columnar epithelium at the beginning soon transforms into pseudostratified columnar epithelium characterized by the cells with nuclei located at different levels depending on the cell cycle phase (Figure 1) [1-3]. At the end of the 3rd week, the lateral ends of the neural plate form the neural folds by raising up. The epithelium of the uppermost cells of the lateral folds is composed of the neural crest which differentiates various neural or non-neural cells and tissues. Between the two neural folds is the neural sulcus (Figure 1). Beginning from the 22nd day neural folds fuse in the midline forming the neural tube that transforms into primitive brain vesicles at the cranial end and spinal cord at the caudal end (Figure 2). Neurulation is a highly complex process including the formation of the neural plate, neural folds, neural sulcus, and finally neural tube; respectively (Figure 1 and 2) [1]. Epithelial tissue remodeling during fusion has been accepted to be characterized by apoptosis in the boundary between neuroepithelium and non-neural ectoderm [4]. The presence of apoptosis at sites of neural fold remodeling may reflect 'anoikis': the triggering of the death pathway in cells deprived of anchorage to other cells or matrix [5]. Once initiated, however, anoikis is not different from apoptosis either biochemically or morphologically, the term

simply emphasizing a particular stimulus for cell death [6]. The neural tube and neuroepithelium give rise to the entire central nervous system cells containing both nerve cells and glial cells [7]. Neural stem/progenitor cells expand as neuroepithelial cells by symmetric proliferative divisions and then at the onset of neurogenesis transform into radial glial cells after switching to asymmetric neurogenic divisions [8]. The radial glial cells generate directly or indirectly all neurons and glial cells [2,9]. Radial glial cells as neuroepithelial cells are highly polarized with their apical membrane exposed to the ventricle and their basal side contacting the pial membrane [2]. As neuroepithelial cells turn into radial glial cells, they downregulate Golgi-derived apical trafficking, and lose tight junctions, initiate to express the astroglial markers such as brain lipid binding protein and glial high-affinity glutamate transporter but maintain adhering junctions [10,11]. Radial glia besides transforming into neurons and glial cells, also acts as scaffold cells for the neurons to migrate over and form the layers of the cortex [12]. Radial glial cells generate neurons by multiple self-renewing asymmetric divisions and newborn neurons often use the parent radial glial cells' fibers to migrate to the upper layers, especially to the cortical plate [13-15]. Radial glial cells have some characteristic apical and basal features to expand throughout the developing cortex and to support the migrating newborn cells. Adhering junctions consisting of cadherins and catenins which anchor to actin molecules mediate intercellular adhesion just basal to the apical plasma membrane. Additionally, polarity proteins including Par3, Par6, and atypical protein kinase C are associated with subapical cytoplasm [16]. At the apical site the centrosome, the nucleation center for the primary cilium, is docked at the apical plasma membrane. The primary cilium is required for detecting signals in the ventricular fluid to maintain the balance between proliferative and differentiative divisions [17-19] and additionally for maintaining proper apicobasal polarity as neuroepithelial cells transform into radial glial cells [20]. The basal side of the radial glial cells is also highly specialized. The basal process of radial glial cell stretching all the way to the basal lamina at the pial surface is important in the maintenance of proliferative capacity through integrin signaling from the basal lamina and via specific basal localization of the G1-S-phase regulator CyclinD2 [21,22]. It is suggested that the evolutionary expansion of neocortical surface area could occur through expanding the radial glia population before the onset of neurogenesis [23,24]. Proliferation and differentiation processes seem to be complicated especially at neurogenesis and late neurogenesis stages.

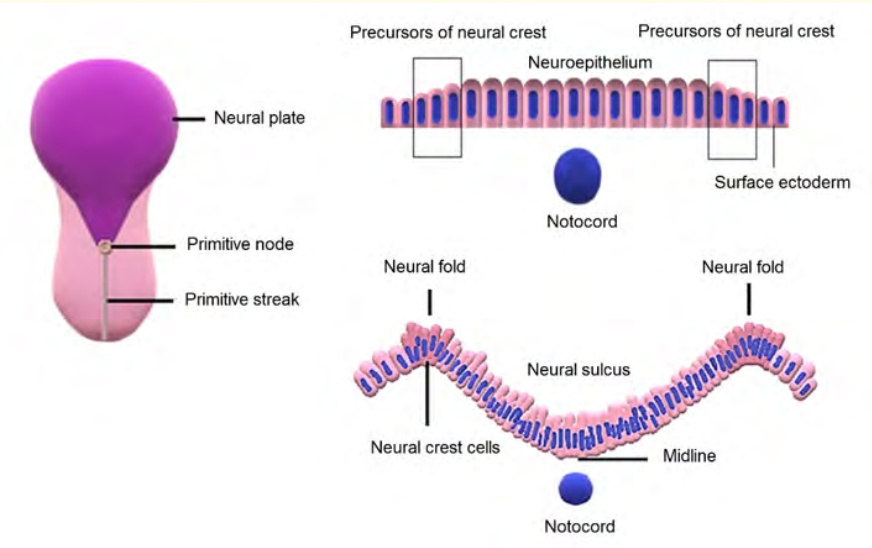


***Figure 1:*** *Formation of the neural folds and sulcus (Drawn by the author herself).*

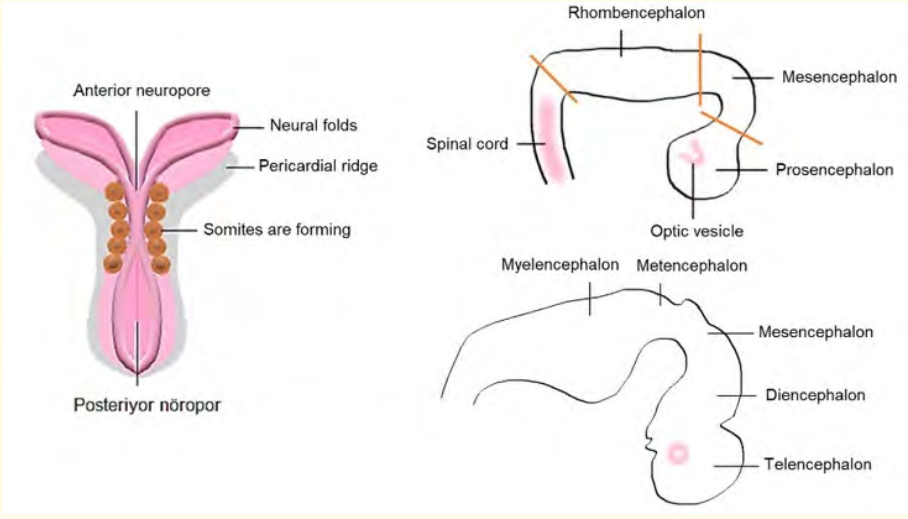


***Figure 2:*** *Formation of the primitive brain vesicles (Drawn by the author herself).*

Before the onset of neurogenesis, symmetric divisions take place within the neuroepithelium. By the symmetric divisions, two daughter neuroepithelial cells are produced by a mother neuroepithelial cell. After the onset of neurogenesis, radial glial cells dividing mainly asymmetrically produce one daughter radial glial cell and one differentiating daughter cell giving rise to a nerve cell eventually. Additional neural progenitor cell types are also formed in the mammalian cortex. One radial glial cell might produce one daughter radial glial cell and one daughter intermediate progenitor which give rise to two nerve cells by symmetrical division eventually. One radial glial cell might produce one daughter intermediate progenitor and one daughter basal radial glial cell which both produce one nerve cell each. One basal progenitor might produce one daughter basal radial glial cell and one daughter intermediate progenitor. During the late neurogenesis period, one radial glial cell might directly produce two nerve cells or two glial cells [2,25] (Figure 3). In the developing vertebrate brain, early radial glial cell division feature cleavage planes perpendicular to the ventricular surface [2]. Oblique and horizontal cleavage planes appearing only in later developmental stages are suggested to generate basal progenitors such as basal radial glia and intermediate progenitors which are important during a cortical expansion [26-29]. During development, several symmetrical and nonsymmetrical divisions take place in the layers of the primitive cortex which are the ventricular zone, subventricular zone, intermediate zone, cortical plate, and marginal zone [1,2] (Figure 4).

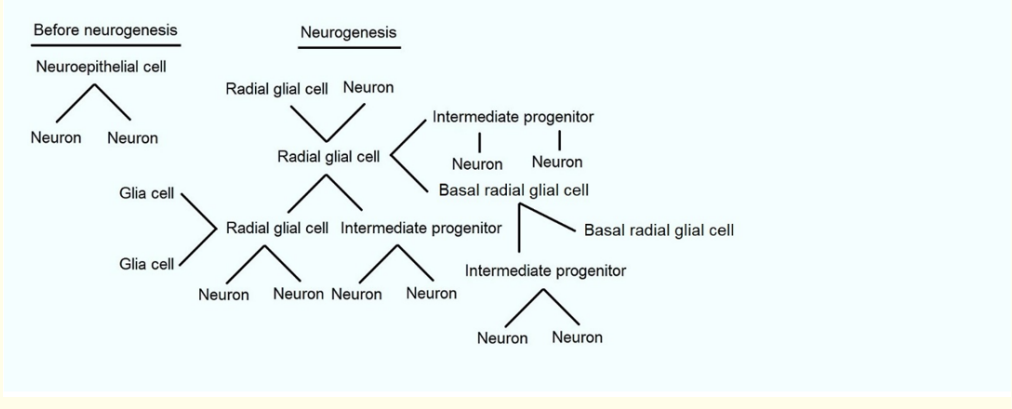


***Figure 3:*** *The main proliferation and differentiation pattern in the nervous system before and after the onset of neurogenesis (Drawn by the author herself).*

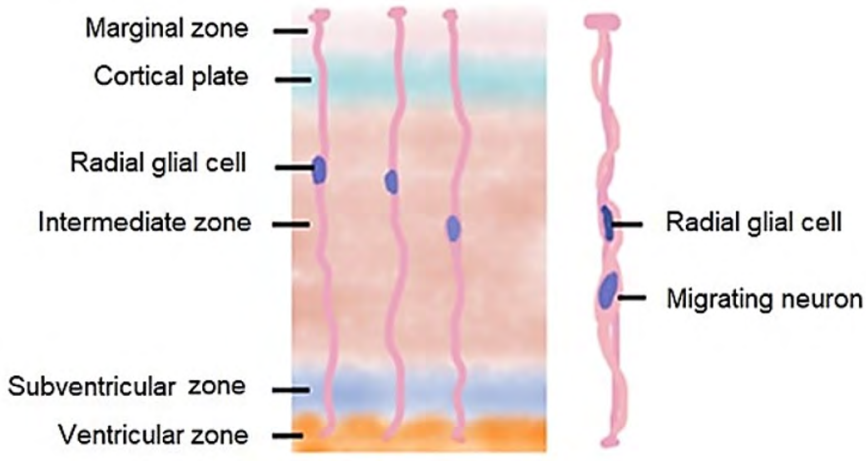


***Figure 4:*** *Primitive histological zones of the brain cortex (Drawn by the author herself).*

## Cell dynamics within neocortex

Precise patterns of cell division and migration are crucial to transform the neuroepithelium of the embryonic forebrain into the adult cerebral cortex which is composed of several layers. Neuroepithelial cells contribute to most of the major cell types including neurons and glial cells. Neurons are generated by the divisions and further differentiation of the progenitor cells of the ventricular zone and subventricular zone. Neurons arise directly from radial glial cells in the ventricular zone and indirectly from intermediate progenitor cells in the subventricular zone. The ventricular zone is considered a site of asymmetrical divisions whereas the subventricular zone is considered a site of symmetrical divisions [12]. In the region of the cerebral cortex, during the neurogenic period, multipotent neural progenitors have recently been found in the form of radial glial cells [13,30]. Consequently, two ways of neuron generation can be distinguished. One is the generation of neurons by the asymmetrical division of radial glial cells, thus ensuring self-renewal and simultaneously producing either a neuron or an intermediate progenitor or alternatively by way of symmetrical division of intermediate progenitor cells [14]. The first formed radial glial cells extend from the base to the subpial area to guide the other cells' migration. Within 5 - 6$^{th}$ weeks, a rapid division occurs in neuronal precursors in the ventricular zone [1,14]. At the onset of the neurogenesis radial glial cells switch from symmetrical to asymmetrical divisions, giving rise to a daughter radial glial cell and a differentiating cell [2]. One daughter cell is associated with self-renewal, and the other daughter progenitor cell usually undergoes one terminal symmetrical division producing two neurons [14]. Thus, one progenitor cell moves to the upper zone, while the other remains in the zone and continues to divide. Towards the end of neurogenesis, cortical progenitors switch back to symmetrical divisions. At this period, while some of the remaining progenitors finishing up the last round of neurogenesis, some others start to produce glial cells [31]. Progenitor cells undergoing prolonged series of symmetric divisions have been suggested to give rise to astrocytes [32]. Young postmitotic neurons wrap around radial glial cells to determine their migration routes [1,14]. Radial glial cells as neuronal progenitor cells in the ventricular zone form an epithelial niche that gives rise to radial clones of neurons through a series of asymmetrical divisions. That organization and division pattern explains the neocortex's radial organization [23,24]. Intermediate progenitors which are also known as basal progenitors have their name derived from their division that occurs distant from the ventricular surface [33]. Prior to the formation of a distinct subventricular zone, intermediate progenitor cells also divide in the ventricular zone [15,34]. Intermediate progenitors are responsible for the production of the majority (> 80%) of pyramidal-projection neurons for all layers, which is against the earlier hypothesis that

intermediate progenitor cells generate only the neurons of the upper layers [35,36]. Studies have defined that the subventricular zone possessing multipolar non-epithelial daughters of radial glia cells, intermediate progenitor cells, is the major site of neurogenesis [14,37]. The fact that the highest numbers of neuron-producing cell divisions are by intermediate progenitors during all stages [34] implies that a major role of radial glial cells in neurogenesis is to make neuronally committed to intermediate progenitors. The increase in the number of intermediate progenitors occupying the same linear position would be more consistent with the tangential expansion of the surface area of the neocortex, whereas an increasing number of asymmetrical divisions of radial glia cells would be more consistent with the expansion of the thickness of neocortex [12]. The outer subventricular zone containing epithelial progenitor cells resembling radial glia cells [38] or transit-amplifying cells resembling intermediate progenitors [39] contributes to neuron production [12]. Unlike bipolar radial glia cells of the ventricular zone, radial glia-like progenitor cells of the outer subventricular zone are unipolar [21]. Although radial glia-like progenitor cells of the outer subventricular zone likely originate from the ventricular zone, they can also expand their number by proliferation within the outer subventricular zone [12,40]. Radial glia-like cells of the subventricular zone which constitute 40% of progenitor cells of that zone most commonly divide asymmetrically to self-renewal regenerating bipolar daughter cells [41]. Many newborn neurons produced within the outer subventricular zone may follow a discontinuous relay of fibers that originate from outer radial glia-like cells of the outer subventricular zone instead of following the direction of a single glial fiber. Thus, neurons disperse horizontally during migration from fiber to fiber [12]. So-called short neural precursors residing in the ventricular zone and dividing at the ventricular surface might represent another class of progenitor cells [42]. These cells possess ventricular contacts via short basal processes that do not extend beyond the subventricular zone. In summary, four main types of cortical progenitors have been identified within the developing cortex: neuroepithelial cells, radial glial cells, intermediate progenitors, and short neural precursors [43]. It has been demonstrated that early-born progenitors have multipotency and can produce both deep and upper-layer neurons, whereas late-born progenitors have significantly more limited options and can only produce upper-layer neurons [44,45].

Neurogenesis of the human neocortex involves multiple stem and transit-amplifying cell divisions. Increased numbers of neurons human neocortex are thought to be achieved by the increased number of founder cells in the form of nonventricular radial glia cells (radial glia-like cells of the outer zone of the subventricular zone), the increased number of intermediate progenitors derived by multiple asymmetrical divisions of nonventricular radial glia cells and finally increased proliferative capacity of intermediate progenitors giving rise to increased numbers of neurons [12].

The association of radial glial cells and surrounding neuroblasts is defined as the columnar radial unit [1,13,46] (Figure 4). An estimated 200 billion radial units are present in the human cerebral cortex [1]. The more than 1000-fold increase in the cortical surface without a similar boom in its thickness during mammalian evolution may be defined as the context of the radial unit hypothesis. Cortical enlargement outcomes from modifications inside the proliferation kinetics of founder cells within the ventricular region increase the variety of radial columnar gadgets without notably changing the number of neurons within every unit. Hence, regulatory genes that manipulate the timing (onset/charge/duration) and mode (symmetrical/asymmetrical) of cell divisions and the importance of apoptosis within the ventricular region decide the range of cortical cells in a given species [47]. In developing monkey and human neocortex, cells with similar morphology to radial glial cells, but located outside of the ventricular zone and not necessarily extending throughout the developing cortex have been found. These cells have been considered as non-ventricular radial glial cell-like cells transforming into astrocytes since no knowledge has not been accumulated that radial glial cells form neurons as well as glial cells at that time [48,49]. These cells might be derived from the radial glial cells which detached from the ventricular zone generating a stellate structure in the parenchyma during the late embryonic and postnatal period [50-52]. Now it is known that radial glial cells generate newborn neurons through multiple rounds of self-renewing, asymmetric divisions [13,14]. They might represent early intermediate progenitor cells [14,15,37]. Nevertheless, newborn neurons do not migrate directly to the cortex; instead, most exhibit four distinct phases of migration, including a step of retrograde movement toward the ventricle before migration to the cortical plate [14].

Neuroepithelial cells and radial glial cells mutually called apical progenitors portray apicobasal polarity, with apical and basal processes that span the neuroepithelium [2]. The nuclei of the pseudostratified neuroepithelial cells are located at different levels depending on the cell cycle stage they are in [3]. Neuroepithelial cells move their nuclei depending on the cell cycle phase. Before division, these cells move their nuclei to the ventricular surface for mitosis [2]. The term 'interkinetic nuclear migration' (IKNM) represents the apical-basal displacement of the nucleus during the cell cycle of ventricular radial glia cells [12,53]. Prior to mitosis, in G2 phase, the nucleus of the radial glial cell moves to the ventricular surface where the centrosome is docked using actomyosin and microtubule motor proteins [54]. Nuclear positioning of the neuroepithelial cells is under the control of the members of the cytoskeleton. Namely, IKNM is dependent on the integrity of both actin filaments and microtubules [55,56]. Recent evidence demonstrates that centrosome and microtubule-associated proteins play a major role in regulating INM [57].

It has been proposed that interkinetic nuclear migration functions to maximize the number of radial glial cell mitosis at the small ventricular surface [54]. Neuroepithelial cell shape is determined by the nuclear position which varies from apical (during mitosis) to basal (during the S phase) due to the process of IKNM [53]. The nuclear movement spans the entire apical-basal axis of the cell. The nucleus migrates to the basal side during the G1 stage of mitosis, stays there during the S stage, migrates back to the apical side during the G2 stage, and finally undergoes mitosis there [3] (Figure 5).

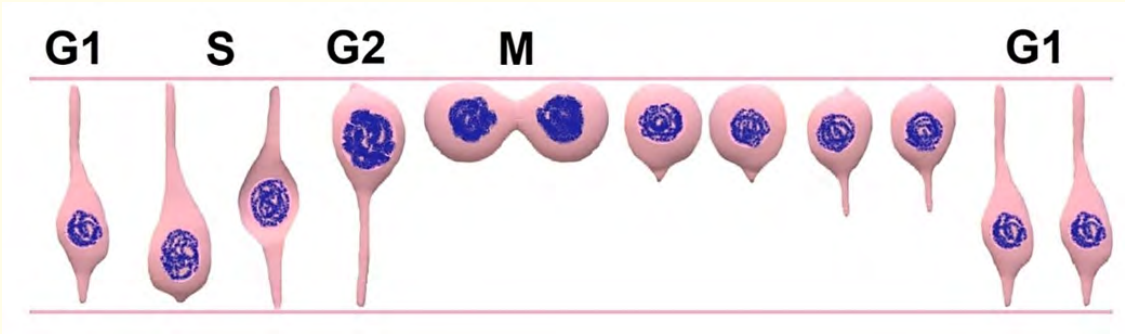


***Figure 5:*** *Scheme of interkinetic nuclear migration (Drawn by the author herself).*

Radial glia-like cells of the outer subventricular zone exhibit a different behavior whereby the cell body rapidly ascends along the radial fiber during the hour preceding cell division, a process termed 'mitotic soma translocation'. These cells undergo multiple rounds of such divisions, suggesting that these divisions are self-renewing and asymmetric and push the boundary of the outer subventricular zone outward. They can be considered neural stem cells based on their multiple rounds of self-renewing asymmetric division, which functionally define them as the building blocks for outer subventricular zone-derived neurons and progenitor cells [12,40].

Delta-Notch signaling pathway takes an important role in regulating neurogenesis. The Notch receptor and its ligands are transmembrane proteins encoded by the so-called neurogenic genes. Due to the interkinetic nuclear migration, neural precursors in the neurogenic state are grouped close to each other, while neural precursors in the pre-neurogenic state are segregated from the former ones. Delta-Notch signaling is maximum in neurogenic precursors resulting in the production of a relatively low number of neurons. In the absence of interkinetic nuclear migration, neurogenic and pre-neurogenic precursors are intermingled. Delta-Notch signaling becomes reduced resulting in an increase in neurogenesis and depletion of neural precursor in the neuroepithelium [3].

## Gliogenesis

After radial glial cells generate neurons, a 'gliogenic switch' occurs and they begin differentiating into astrocytes or oligodendrocyte precursor cells (OPCs, also called NG2 glia because they Express NG2 proteoglycan on the surface) [58-60]. Little is known about the mechanisms underlying the temporal switch made by neural progenitors from neurogenic to gliogenic either *in vivo* or *in vitro*. Both intrinsic and extrinsic factors may control this neurogenic to gliogenic switch [31]. In recent years, evidence has emerged that epigenetic modifications such as DNS methylation and histone modifications are involved in the control of temporal and spatial gene expression during neurogenesis, and switch from neural to glial production [43]. Numerous secreted signals - notably Sonic hedgehog (Shh), fibroblast growth factors (FGFs), Wnts, Notch/Delta, bone morphogenetic proteins (BMPs), and cytokines - act together to control cell fate spatially and temporally, leading to the presence of specific domains that selectively generate either astrocytes or OPCs [58,59]. Key transcription factors involved at this time include Sox9, nuclear factor-I and serum response factor for general gliogenesis, and Olig1/Olig2 for OPC production [58,61]. During *in vivo* development, differentiated neurons are proposed to communicate with progenitors in a negative feedback manner to instruct progenitors to switch from a neurogenic to a gliogenic state [62]. After the neurogenic period is over, gliogenesis supersedes neurogenesis at late embryonic or perinatal stages [63]. The majority of cortical neurogenesis occurs prior to birth, while gliogenesis is a perinatal and postnatal phenomenon [64,65]. Many factors have been implicated, directly or indirectly, in gliogenesis regulation including Sox9, Notch signaling, the transcriptional repressor N-CoR, the methylase Dnmt1, and histone methylation [66,67].

In addition to multipotent progenitors which give rise to all three lineages including neurons, astrocytes, and oligodendrocytes, bipotential progenitors for astrocytes and neurons or oligodendrocytes and neurons are present in the developing central nervous system. Common progenitors capable of producing both astrocytes and oligodendrocytes are rarely observed [68]. However, according to recent studies, glial and even neuronal progenitor cells are able to return to multi- or bipotent progenitor states and subsequently produce both neurons and glia under optimal conditions [69-71]. An interesting recent body of work has raised the possibility that astrocytes may retain a limited, perhaps vestigial capacity to re-acquire stem cell properties by de-differentiating in response to reprogramming or certain types of brain injury [72]. Several *in vitro* studies suggested that certain transcription factors such as Pax6 [73] or combinations of ng2/mash1 could form neurons [74]. *In vivo*, astrocytes were re-programmed to generate neurons by re-expressing three transcription factors [75]. Perhaps glia, in their expertise in 'listening to' and 'talking to' neurons are inherently plastic in a variety of ways- epigenetic, morphological, and functional [72].

Astrocyte production from radial glial cells in the developing cortex occurs in two waves. In the first wave, radial glial cells produce glial progenitors by asymmetrical divisions. These progenitors migrate radially from the ventricular and subventricular zone, undergo several mitoses on their way out, and give rise to multiple clusters of astrocytes [76,77]. It is suggested that progenitor cells undergoing prolonged series of symmetric divisions produce astrocytes [32]. The second wave which occurs at the terminal stage of differentiation results from the direct transformation of radial glial cells [78]. It has been suggested that radial glia may transform into astrocytes in their terminal division, perhaps counting for the 10 - 15% of astrocytes generated from even primarily oligodendrogliogenic domains [58,79].

Between the late embryonic and early perinatal stages, radial glial cells detach their anchorage from the ventricular zone and lift their soma toward the pial surface. These unipolar radial glial cells undergo terminal differentiation to produce protoplasmic and fibrous astrocytes [78]. Spinal cord astrocytes are derived from the ventricular zone (VZ), whereas forebrain astrocytes are from the ventricular–subventricular zone [80]. Before terminal differentiation, astrocyte precursors migrate from the ventricular zone and subventricular zone along the radial glial processes. Newborn astrocytes continue to divide locally after the migration [78]. The authors found that local division (after astrocyte precursor migration) generates about half of the mature cortical astrocytes, although when this proliferation takes place is not exactly clear. Most likely, astrocytes and their precursors at multiple developmental stages coexist in the developing cortex

[72]. As the white matter develops postnatally, astrocytes mature into fibrous and protoplasmic subtypes, the two major morphological divisions historically [81]. So far, members of the EGF family (TGF-b and HBEGF), Wnt7a, FGFs, and BMPs have all been shown to promote astrocyte process formation *in vitro* [82,83].

As mentioned above, as astrocytes, oligodendroglia cells are also produced by the radial glial cells. They presumably arise by the division of radial glial cells in the ventricular zone, with one daughter cell retaining contact with the ventricular and pial surfaces and the other daughter cell which is the oligodendrocyte precursor cell itself losing those contacts [84]. Oligodendrocyte precursor cells can be detected in the ventricular germinal zones of the brain and spinal cord around mid-gestation in rodents. In humans, these cells appear in the ventral floor plate around gestational week 6.5 [84,85]. Notch signaling pathway collaborates with Shh for oligodendroglia precursor cell specification [60]. In the zebrafish ventral neural tube, Notch signaling between committed neuronal precursors and radial glia keeps the latter in a stem-like state, thereby preserving the pool of precursors available to generate OPCs later [86,87]. Notch signaling also plays an important role later during development, when oligodendroglia precursor cells are maturing to oligodendroglia cells and elaborating myelin [88].

## Conclusion

Cell diversity, proliferation, differentiation, and migration patterns, influential factors in neurogenesis and gliogenesis are quite complex and sometimes confusing. The neuroepithelial cells contribute to the major cell types including neurons and glial cells including astrocytes and oligodendroglia cells. Microglia are neural cells of nonneural origin; they originate from fetal macrophages that invade the neural tube early in embryogenesis. On the other hand, the last glial cell type which is the ependymal cells are the original cells of the neuroectoderm. Since it is impossible to conduct experimental studies in human embryos, valuable data on proliferation, differentiation, and migration characteristics in the neuroepithelium is obliged to be obtained through animal experiments.

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