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Editorial

Proliferating Astrocytes in Developing Brain and Reactive Astrocytes in Neurological Disorders

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Editorial

The neonatal astrocytes used to be considered a population of stage specific, proliferating immature astrocytes. Over the course of brain maturation, the newly generated astrocytesundergo extensive changes in gene expression, form spatially exclusive domains, connect through gap junctions into a syncytial network, and interact with and envelop blood vessels as part of the blood brain barrier [1-8]. Over the past two decades, increasing evidence shows that the very same "immature" astrocytes are the sculptors of synaptogenesisand facilitators of myelination in the CNS [8-10].

Interestingly, similar to proliferating neonatal astrocytes, various neuropathlogical disorders stimulate mature astrocytes to reenter the cell cycle for proliferation. The disease conditions also alter the morphology of differentiated astrocytes, disrupt well-established gap junction coupling and syncytial organization of astrocytic networks, and induce changes in gene expression and functional properties [11,12]. A hypothesis that remains to be tested is whether reactive astrocytesindeed recapture the gene expression profile and functional phenotype of neonatal astrocytes. An answer to this question is important because exciting discoveries are emerging from neonatal astrocytes that may shed new light on the development of a therapeutic strategy for disease treatment.

Proliferating Astrocytes in Postnatal Brain Are Diverse in Origin

Astrocytes are the last cellular constitute generated in the brain. In various regions of the rodent brain, their generation occurs around birth (E20-P3). This first cohort of astrocytes mainly arises from direct transformation of Ventricular Zone (VZ) radial glia and asymmetric division of glial progenitor cells [13-19]. After a short dormant period [4], the second cohort of astrocytes is mainly produced through symmetric division of differentiated astrocytesand to a less extent asymmetric division of NG2 glia in the ventrolateral forebrain [5,20]. In contrast to neurons that are majorly produced before the birth, there is a 6-8 fold increase in the number of astrocytes in the postnatal developing brain.

Functional Diversity of Astrocytes Generated in Early and Late Postnatal Brain

While a universal marker for identification of astrocytes in the developing and adult brain is still unavailable [10], our recent study confirmed that the eGFP in ALDH1L1-eGAP transgenic mice and a chemical marker SR101 can be reliably used to identify neonatal astrocytes in mouse hippocampal *stratum radiatum* [24]. In this study, astrocytes generated from P1-3 are electro physiologically homogeneous. Specifically, these neonatal astrocytes express a distinct set of rectifying K^+channel conductance's, namely, depolarization-induced voltage-gated outwardly transient (IK_a), delayed rectifying (IK_d), and inwardly rectifying (IK_{in}) conductance. This differs from the linear passive conductance of mature astrocytes [25]. Also, astrocytes generated around birth exhibit a more negative membrane potential (V_M) than astrocytes in the adult brain. Importantly, astrocytes produced in the P8-13 cortex through symmetric cell division share the same electrophysiological features as astrocytes in the adult brain [5]. This indicates strongly that proliferating astrocytes in the postnatal brain are functionally diverse.

It is also of great interest to know that neither proliferating astrocytes nor astrocytes in the adult brain express voltage-gated Na^+channel current (IN_a), whereas IN_a is a characteristic of NG2 glia in the developing and mature brain [26-28]. Thus lack of INa appears to be diagnostic for differentiating astrocytes from NG2 glia.

The difference in IK_{in} expression between early and later proliferating astrocytes is directly relevant to the function of these astrocytes. We show that a 6-fold lower inward K^+ current density in P1-3 astrocytes is associated with a 50% deficiency in K^+buffering capacity compared to mature astrocytes [24]. As will be discussed later,P1-3 astrocytes also lack a maturely established syncytium to achieve a "sustained K^+ uptake" mode that would further undermine the K^+uptake and spatial

redistribution in the neonatal brain [29]. How the observed difference in K^+ conductance and gap junction coupling would be etiologically relevant to neurological disorders in the neonatal brain is yet unknown.

Proliferating Astrocytes form Discrete Gap Junction Coupling in the Early Postnatal Brain

In the neonatal brain, astrocytes converge from difference sources. The question of how the nascent astrocytes connect with each other through gap junctions in their early life has been recently answered [24]. It appears that newborn astrocytes in the embryonic and early neonatal brain are initially in isolation, but quickly establish cell-to-cell coupling with neighboring astrocytes, because the percentage of coupling astrocytes increases rapidly from P1-3.

Interestingly, in the P6-13 postnatal cortex, locally produced astrocytes are electrically passive, functionally mature and integrated into a network during symmetrical cell division [5]. These independent observations again indicate that proliferating astrocytes in the postnatal brain should not be treated as a homogeneous population of stage-specific cell population.

Proliferating Astrocytes and Reactive Astrocytes in Neurological Disorders

The proliferating astrocytes in the neonatal brain seemingly recapture the characteristics of reactive astrocytes observed in several pathological conditions. First, similar to proliferating neonatal astrocytes, reactive astrocytes reenter the cell cycle for proliferation [30]. Second, proliferating reactive astrocytes show virtually no gap junction coupling in dye coupling analysis [30] third, only neonatal proliferating astrocytes predominantly express voltage-gated ion channels, which is consistent with the altered expression of K^+ conductance in lesion-induced reactive astrocytes [31-33]. Voltage-gated K^+ channels have been demonstrated to play a role in cell cycle progression [34].

Nevertheless, reactive astrocytes are characterized by alteration of astrocyte gene expression and morphology in a context-specific manner through intrinsic and extrinsic cellular signaling mechanisms. An emerging view of astrogliosis is that different pathological stimuli result in a heterogeneous population of reactive astrocytes, which is not an all-or-none phenomenon, but rather a graded continuum change ranging from gene/protein expression to cellular morphology/function. Astrogliosis can also lead to either a gain-of-function or loss-of-function. Thus, the characteristics of diversity of proliferating astrocytes may serve as an important foundation for further examination into the extent to which reactive astrocytes recapture the features of neonatal astrocytes and their pathological and therapeutic implications [35-37].

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