News Release

Title

Unified control of neuronal delamination and outer radial glial cell generation during mammalian cerebral development

Key Points

○ Lzts1 positively controls both neuronal delamination and outer radial glial cell generation during mammalian cerebral development.

○ Lzts1 is strongly expressed at the adherence junction of the nascent neuronally differentiating cells and induces rapid delamination.

○ Weakly-expressed Lzts1 in the apical radial glial cells induces the oblique division to generate outer radial glial cells.

Summary

Research Assistant Professor Takumi KAWAUE, Associate Professor Ayano KAWAGUCHI in Department of Anatomy and Cell Biology, Nagoya University Graduate School of Medicine (Dean: Kenji KADOMATSU, M.D., Ph.D.), Dr. Fumio MATSUZAKI in RIKEN Center for Biosystems Dynamics Research and Graduate School of Biostudies, Kyoto University, and their collaborators experimentally demonstrated the molecular mechanism controlling both neuronal delamination and outer radial glial cell generation during mammalian cerebral development.

In the developing central nervous system, cell departure from the apical surface is the initial and fundamental step to form the 3D, organized architecture. Neuronal delamination and repositioning of progenitors to generate outer radial glial cells (oRGs) are two major pathways to depart from the apical surface. Both cellular events contribute to mammalian neocortical expansion; however, a comprehensive understanding of their mechanisms is lacking. The research group demonstrated that Lzts1, a molecule associated with microtubule components, promotes these cell departure events in an expression level-dependent manner. Their findings suggest that Lzts1 functions as a master modulator of the cytoskeleton, including both the actomyosin system and microtubules, to produce diverse cell behaviors in the cell departure processes.

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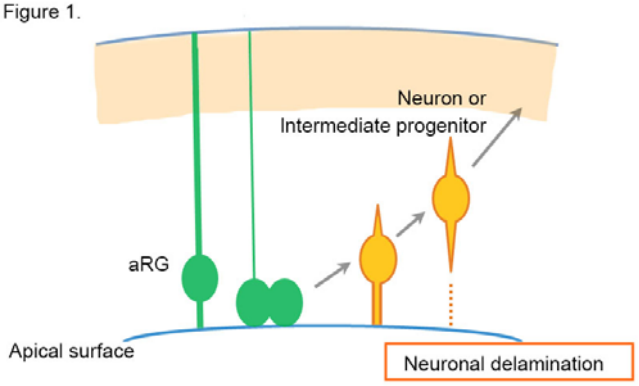
Research Background

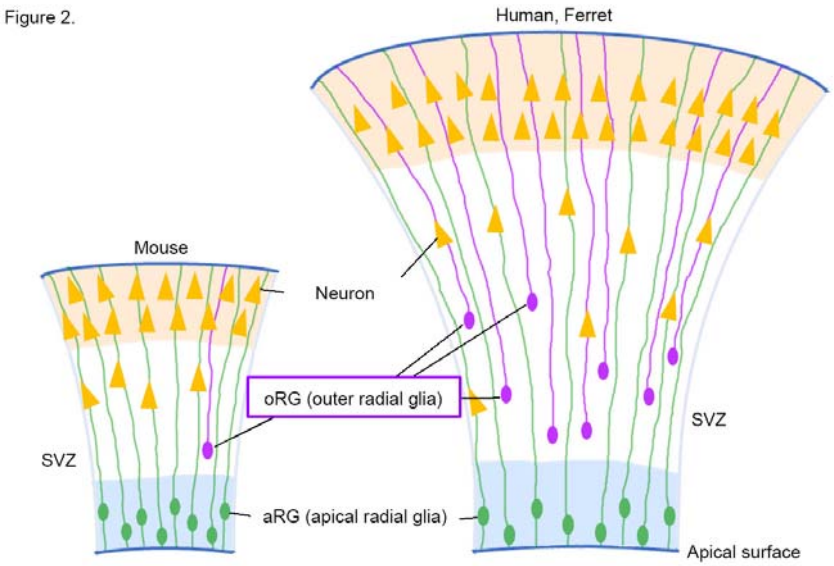
During mammalian neocortical development, radially elongating apical radial glial cells (aRGs) divide to produce two daughter cells at the apical surface. Two major pathways have been identified for daughter cells to disconnect and depart from the apical surface. One is neuronal delamination by cells committed to differentiate into the neuronal lineage (Figure 1), and the other is oblique division related to the generation of outer radial glial cells (oRGs). oRGs are undifferentiated neural progenitor cells that divide multiple times in the subventricular zone (SVZ). These cells are more abundant and proliferative in the species with gyrencephalic brains, such as humans and ferrets, than in mice with lissencephalic brains, indicating that the cell departure process that repositions the neural progenitors is also critical for the evolutionary expansion of the neocortex (Figure 2). Previous studies have shown that oRGs are typically produced by the oblique (or perpendicular) division of a subset of aRGs and exhibit a unique cellular behavior, mitotic somal translocation (MST) in which the soma rapidly translocates basally before cytokinesis.

Figure 1.



Although these cell departure events are the initial and critical step to form the 3D organized brain, researchers have not clearly elucidated the mechanism by which only differentiating cells delaminate from the apical surface within several hours after birth, and further, the regulatory mechanisms that evoke oblique division of aRG and MST to generate oRGs.

Figure 2.



Research Results

The research group has found that *lzts1* is expressed in a subset of aRGs and all of the neuronally differentiating cells (nascent neurons and intermediate progenitor cells) in the mouse brain at the mid-embryonic stage. They also found that anti-Lzts1 antibody staining was particularly strong at the apical endfeet of the neuronally differentiating cells. Lzts1 immunolabeling by electron

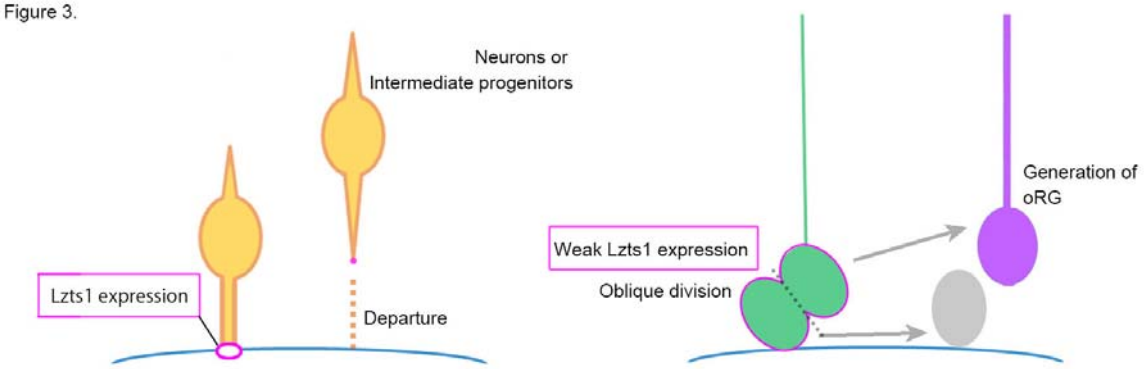
microscopy showed intracellular gold particles that were closely associated with the AJ belts, suggesting that Lzts1 may interact with AJ-related proteins.

By gain-of-function and loss-of-function studies of Lzts1, the authors revealed that Lzts1 ensures rapid neuronal delamination by the apical contraction with downregulation of N-Cadherin (Figure 3, left). Notably, the forced-expression of Lzts1 in the cortical cells by *in vivo* electroporation often induces MST, which is known as a typical cell behavior of oRGs.

Then, the authors have found that weak expression of Lzts1 induces the oblique division of aRGs and that loss-of-lzts1 decrease the frequency of the oblique division. Since previous studies have shown that oRGs are typically produced by the oblique division, the research group examined whether Lzts1 is involved in the oRG generation. They found that loss-of-lzts1 in the mouse embryonic brains and ferret brains by in vivo electroporation reduces the oRG generation (Figure 3, right).

These results indicate Lzts1 controls both neuronal delamination and oRG generation in the developing cerebrum. Such unified regulation of the cell departure events by Lzts1 would ensure the generation of oRGs with neurogenic potential within the time window of neurogenesis.

Figure 3.



Research Summary and Future Perspective

The research group reports that Lzts1 positively controls both neuronal delamination and oRG generation in an expression level-dependent manner. These findings support the hypothesis that these different events are both aspects of the same process, continuously varying cellular dynamics controlled by Lzts1. Future investigations will determine how Lzts1 coordinates dynamic cytoskeletal remodeling to regulate both neuronal delamination and mitotic spindle orientation.

The authors also found that forced expression of Lzts1 in the mouse brain gives rise to MST from the apical surface. Interestingly, a similar cell behavior has been reported in ferrets and humans, but not in mice. These results raise the intriguing possibility that Lzts1 expression or function is enhanced in ferret and human neural progenitor cells and might explain why the frequency and distance of MST and oRG generation are greater in human and ferret brains than in mouse brains; these processes contribute to the evolutionary expansion of the neocortex.

Publication

‘Lzts1 controls both neuronal delamination and outer radial glial-like cell generation during mammalian cerebral development’

Kawaue T[1], Shitamukai A[2], Nagasaka A[1], Tsunekawa Y[2], Shinoda T[1], Saito K[1], Terada R[1], Bilgic M[2, 3], Miyata T[1], Matsuzaki F[2, 3] and Kawaguchi A[1]*.

(* Corresponding author)

[1] Department of Anatomy and Cell Biology, Nagoya University Graduate School of Medicine

[2] Laboratory for Cell Asymmetry, RIKEN Center for Biosystems Dynamics Research

[3] Graduate School of Biostudies, Kyoto University

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