Natural selection among neural progenitor cells controls mammalian brain size

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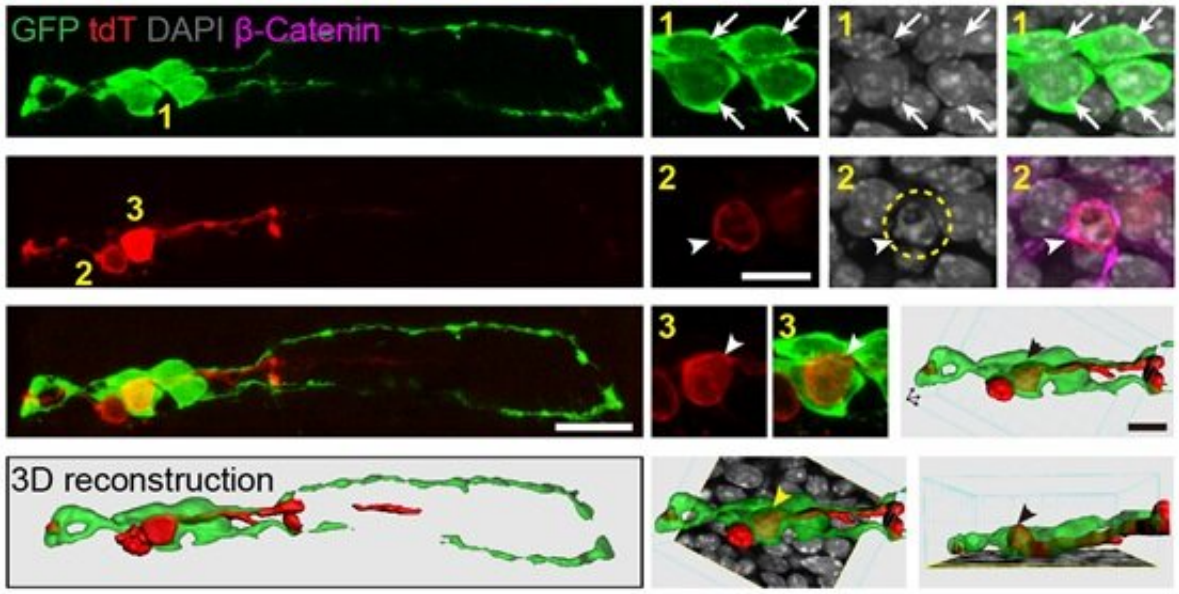

Cell competition between sister neural stem/progenitor cells in mosaic environment. Credit: IGDB

In nature, competition for survival among organisms or species is a fundamental evolutionary force, as described by Darwin's theory of natural selection. Similarly, in multicellular organisms, competitive interactions also occur between cells, creating a cell selection mechanism that eliminates less fit cells within the local tissue environment.

In a study published in *Developmental Cell*, a group led by Prof. Wu Qingfeng from the Institute of Genetics and Developmental Biology

(IGDB) of the Chinese Academy of Sciences demonstrated the presence of cell competition between neural progenitor cells (NPCs) during neurodevelopment.

Cell competition was first described in Drosophila by Prof. Ginés Morata in 1975 and has been extensively studied in this model organism for the past five decades. However, the occurrence and significance of cell competition in mammals has been poorly understood.

Wu and his team systematically investigated the potential regulators, spatial properties, molecular features, mechanism and physiological role of cell competition between NPCs. Besides, opening up new avenues for promoting neuronal fitness and brain health, this research may also establish an important experimental paradigm for interrogating cell competition during neurodevelopmental processes and in neurodegenerative diseases.

To investigate cell competition between NPCs, the researchers first developed a novel strategy for genetic mosaic induction and clonal tracking based on a dual-color labeling system. This approach enabled the researchers to induce genetic mosaicism in NPCs, allowing NPCs to carry different fluorescent proteins, and to track cell fate during the developmental continuum.

Using this method, they identified two key regulators, Axin2 and p53, which are involved in driving cell-cell competitive interaction. Specifically, Axin2-mutant stem cells were eliminated and even engulfed, whereas p53-deficient stem cells underwent clonal expansion in the mosaic environment and became winner cells.

To determine whether cell competition naturally occurs in the developing brain, the researchers collected more than 1,000 mouse brains with clonal labeling of NPCs and studied their fate using short-

and long-term lineage tracing.

The results indicated a cellular ecological hierarchy, wherein the top 10% of proliferative NPCs yielded 30%–40% of progeny neurons, whereas the bottom 10% of NPCs produced only 1%–2% of neurons for the brain. Notably, stem cells that were eliminated at an early developmental stage had no chance of contributing any cells to adult organs.

To gain deeper insight, the researchers generated phenotype-, genotype- and transcriptotype-dependent datasets through single-cell and bulk RNA sequencing, developed a loser signature scoring system and identified the molecular characteristic of loser cells. Application of the scoring system revealed that the loser status of individual NPCs was negatively correlated with Axin2 expression levels, but positively associated with activation of the p53 signaling pathway as well as stress response and protein folding.

Since the inherent differential expression of cell competition drivers is what triggers the competitive interaction and natural selection of NPCs, the researchers determined to ameliorate cell competition by reducing the expression of these drivers to the same level. Their findings showed that this manipulation caused a significant enlargement of brain size and a remarkable rise in the number of neurons, indicating the survival of otherwise unfit stem cells during development.

This work elucidates the drivers, properties, molecular features and physiological function of cell competition in the context of neural stem/progenitor cells during early neurodevelopment. The identification of endogenous cell competition among NPCs provides a fundamental basis for comprehending the developmental origin of neuronal vulnerability as well as improving brain health.

This work also highlights the physiological role of cell competition in regulating mammalian organ size. Identifying this role has been a major challenge despite years of research, especially since most cell competition models are experimentally induced.

More information: Xue-Lian Sun et al, Stem cell competition driven by the Axin2-p53 axis controls brain size during murine development, *Developmental Cell* (2023). DOI: 10.1016/j.devcel.2023.03.016

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