RESEARCH HIGHLIGHT

# Human adult hippocampal neurogenesis is back, again?

Hai-Kun Liu[1] ✉



*Cell Research* (2022) 32:793–794; https://doi.org/10.1038/s41422-022-00698-8

**Whether neurogenesis occurs in the adult human hippocampus is a very controversial issue. Now Wang et al. provide new supporting evidence of newborn neurons in the aged human hippocampus**.

Human adult hippocampal neurogenesis (AHN) is one of the most debated scientific topics in recent years. Since the identification of active neurogenesis in the adult human hippocampus,[1] the field obtained tremendous progress in the molecular regulation and functional relevance of AHN. However, recent debates on whether AHN does exist in the human brain brought this field back into the spotlight.[2–7] The heavily disputed aspects include specificity of marker antibodies and experimental procedures used to detect adult neurogenesis, as well as variations between human brain samples used in those studies.

Therefore, it was suggested from both sides that single-cell RNA-seq (scRNA-seq) may help resolve the controversy, because it is quantitative, less biased and the quality controls are well established.[4,7] Using single-nuclear RNA-seq (snRNA-seq), one recent study reported the lack of molecular signatures of AHN in human hippocampus, whereas the AHN molecular signature could be detected in macaque hippocompus.[5] Another snRNA-seq study analyzed human hippocampi from epilepsy patients and found a possible cell cluster similar to granular precursor cells,[8] although this study did not focus on searching for adult neurogenesis. In a recent study published in *Cell Research*, Wang et al. reported that, also using snRNA-seq, they could identify neural stem cells (NSCs) and active AHN in both macaque and human adult hippocampi. The authors first performed snRNA-seq of macaque hippocampi across the lifespan from early postnatal stage to 23 years old (Y23). They identified cell clusters resembling NSCs and newborn neurons across the macaque lifespan, although the mitotic activity and level of neurogenesis decline with age, which is known in rodent. In addition, Wang et al. identified ethanol phosphate phospholyase (ETNPPL) as a primate-specific NSC marker. Interestingly, the authors discovered an astrocyte population with inflammatory signatures in aged macaque hippocampus, and they suggest that the increase of neuroinflammation may contribute to the age-related decline of AHN.

The authors next performed snRNA-seq in aged human hippocampi (Y67, Y85, Y87, and Y92); they could identify quiescent NSCs, a small population of active NSCs and immature neurons out of 22,119 sequenced nuclei. The authors also performed single-cell ATAC-seq to confirm that NSCs and immature neurons could be identified in aged human hippocampi and found that NSCs and immature neurons are enriched for Sox2 and NeuroG2 binding motifs, respectively. This further supports the authors' claim that active AHN exists in aged human hippocampi, which they further confirmed via immunohistochemistry analysis, using traditional markers as well as markers newly identified in this study. It is important to note that the authors also found variations in the numbers of immature neurons detected among the human samples. To investigate why the previous study failed to detect immature neurons, the authors analyzed the snRNA-seq data from Franjic et al.[5] and found that there is an increase of neuroinflamation signaure and this may provide a possible explanation why immature neurons could not be found in those samples.

The results of Wang et al. provide supporting evidence for active AHN in humans and suggest that the increased inflammation in human brain may contribute to the decline of AHN, which is consistent with the rodent study.[9] This may also help understand the variation of newborn neuron numbers found in human studies. The data provided here can serve as an important resource to better understand the debate of the existence of AHN in the aged human brains.

Based on the currently available data, it is clear that scRNA-seq analysis of human hippocampus will not easily resolve the controversy, and it is foreseeable that the dispute will continue in the next years. More well-controlled high-quality human samples across a wide human lifespan, as well as samples from different disease backgrounds will be needed to overcome the big variation in human studies. Moreover, it is important to note that scRNA-seq analysis is descriptive and does not provide direct evidence of active AHN in human brain. There are a few outstanding questions that the field needs to address with further technical advances, like how to demonstrate active cell proliferation and ongoing neurogenesis in the human brain independent of the descriptive histological analyses? This may require application of lineage tracing analysis of human hippocampus using endogenous genetic sequences.[10] How to prove and disprove the existence of quiescent or dormant NSCs in the adult human brain? It is likely that increase of inflammation induces NSC dormancy, but how to assess whether these cells are indeed stem cells and how to determine whether these cells can be activated under certain conditions? Is somatic clonal expansion involved in regulation of NSC heterogeneity? Somatic clonal expansion during aging is well documented in several human tissues, particularly in the hematopoietic stem cells.[11] Emerging evidence demonstrates that this may also happen in the human brain.[12] If active AHN does occur throughout the human long lifespan, it is likely that clonal neurogenesis will occur in neural cell populations with a lifelong mitotic history. It was also reported that cells harbor tumorigenic mutations could be found in another suspected adult

[1]Division of Molecular Neurogenetics, German Cancer Research Center (DKFZ), DKFZ-ZMBH Alliance, Im Neuenheimer Feld 280, Heidelberg, Germany.
✉email: L.Haikun@Dkfz-Heidelberg.de

Published online: 18 July 2022

human neurogenic area.[13] Therefore, analysis of human brain genetic mosaicism in the suspected neurogenic areas may help clarify the existence of adult human neurogenesis. Most importantly, it would be encouraging if the experts in the field, irrespective of their personal opinions on this topic, could come together and define what scientific investigations are necessary and sufficient to help resolve the controversy in a more conclusive way. This is not only beneficial for the development of this field, what is even more important is that the field could set a good example of how to constructively solve a scientific debate for the next generation of young scientists.

## REFERENCES

1. Eriksson, P. S. et al. *Nat. Med.* **4**, 1313–1317 (1998).
2. Moreno-Jiménez, E. P., Terreros-Roncal, J., Flor-García, M., Rábano, A. & Llorens-Martín, M. *J. Neurosci.* **41**, 2541–2553 (2021).
3. Sorrells, S. F. et al. *J. Neurosci.* **41**, 2554–2565 (2021).
4. Kempermann, G. et al. *Cell Stem Cell* **23**, 25–30 (2018).
5. Franjic, D. et al. *Neuron* **110**, 452–469 (2022).
6. Terreros-Roncal, J. et al. *Science* **374**, 1106–1113 (2021).
7. Paredes, M. F. et al. *Cell Stem Cell* **23**, 780–781 (2018).
8. Ayhan, F. et al. *Neuron* **109**, 2091–2105 (2021).
9. Ekdahl, C. T., Claasen, J.-H., Bonde, S., Kokaia, Z. & Lindvall, O. *Proc. Natl. Acad. Sci. USA* **100**, 13632–13627 (2003).
10. Ludwig, L. S. et al. *Cell* **176**, 1325–1339 (2019).
11. Jaiswal, S. & Ebert, B. L. *Science* **366**, eaan4673 (2019).
12. Ganz, J. et al. *Cancer Discov.* **12**, 172–185 (2022).
13. Lee, J. H. et al. *Nature* **560**, 243–247 (2018).

## ACKNOWLEDGEMENTS

H.-K.L. is supported by the Deutsche Krebshilfe (110226), the ERC (European Research Council) (647055), the Deutsche Forschungsgemeinschaft (SFB1389, UNITEGLIOBLASTOMA) and the DKTK (German consortium for translational cancer research, AIM2GO).

## ADDITIONAL INFORMATION

**Correspondence** and requests for materials should be addressed to Hai-Kun Liu.