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Tracing the Evolution of the Cerebellum

Heidelberg scientists unveil genetic programmes controlling the development of cellular diversity in the cerebellum of humans and other mammals. The research results have now been published in the journal Nature.

The evolution of higher cognitive functions in human beings has so far mostly been linked to the expansion of the neocortex – a region of the brain that is responsible, inter alia, for conscious thought, movement and sensory perception. Researchers are increasingly realising, however, that the "little brain" or cerebellum also expanded during evolution and probably contributes to the capacities unique to humans, explains Henrik Kaessmann from the Center for Molecular Biology of Heidelberg University (ZMBH). His research team has now – together with Stefan Pfister from the Hopp Children's Cancer Center Heidelberg (KiTZ) – createdgenerated comprehensive genetic maps of the development of cells in the cerebella of humans, mice and opossums. Comparisons of these data reveal both ancestral and species-specific cellular and molecular characteristics of cerebellum development spanning over 160 million years of mammalian evolution.

"Although the cerebellum, a structure at the back of the skull, contains about 80 percent of all neurons in the whole human brain, this was long considered a brain region with a rather simple cellular architecture," explains Henrik Kaessmann. In recent times, however, evidence suggesting a pronounced heterogeneity within this structure has been growing, says the molecular biologist. The Heidelberg researchers have now systematically classified all cell types in the developing cerebellum of humans, mice and opossums. To do so they first collected molecular profiles from almost 400,000 individual cells using single-cell sequencing technologies. They also employed procedures enabling spatial mapping of the cell types.

On the basis of these data the scientists noted that in the human cerebellum the proportion of Purkinje cells – large, complex neurons with key functions in the cerebellum – is almost double that of mice and opossums in the early stages of foetal development. This increase is primarily driven by specific subtypes of Purkinje cells that are generated first during development and likely communicate with neocortical areas involved in cognitive functions in the mature brain. "Accordingly, it is tempting to speculate that the expansion of these specific types of Purkinje cells during human evolution supports higher cognitive functions in humans," explains Mari Sepp, a postdoctoral researcher in Kaessmann's research group "Functional evolution of mammalian genomes".

Using bioinformatic approaches, the researchers also compared the gene expression programmes in cerebellum cells of humans, mice and opossums. These programmes are defined by the fine-tuned activities of a myriad of genes that determine the types into which cells differentiate in the course of development. The scientists identified genes with cell-type-specific activity profiles that have been conserved across species for at least about 160 million years of evolution. According to Henrik Kaessmann, this suggests that they are important for fundamental mechanisms that determine cell type identities in the mammalian cerebellum. At the same time, the researchers identified over 1,000 genes with activity profiles differing between humans, mice and opossums. "At the level of cell types, it happens fairly frequently that genes obtain new activity profiles. This means that ancestral genes, present in all mammals, become active in new cell types during evolution, potentially changing the properties of these cells," says Kevin Leiss, who – at the time of the studies – was a doctoral student in Kaessmann's research group.

Among the genes showing activity profiles that differ between humans and mice – the most frequently used model organism in biomedical research – several are associated with neurodevelopmental disorders or childhood brain tumours, Stefan Pfister explains. He is a director at the KiTZ, heads a research division at the German Cancer Research Center and is a consultant paediatric oncologist at Heidelberg University Hospital. The results of the study could provide valuable guidance in the search for suitable model systems – beyond the mouse model – to further explore such diseases, suggests Pfister.

The research results were published in the journal "Nature". Also participating in the studies – apart from the Heidelberg scientists from the ZMBH and the KiTZ – were researchers from Berlin as well as China, France, Hungary, and the United Kingdom. The European Research Council financed the research. The data are available in a public database.

Publication:

M. Sepp, K. Leiss, F. Murat, K. Okonechnikov, P. Joshi, E. Leushkin, L. Spänig, N. Mbengue, C. Schneider, J. Schmidt, N. Trost, M. Schauer, P. Khaitovich, S. Lisgo, M.

Palkovits, P. Giere, L. M. Kutscher, S. Anders, M. Cardoso-Moreira, I. Sarropoulos, S. M. Pfister, and H. Kaessmann: Cellular development and evolution of the mammalian cerebellum. Nature 2023, https://doi.org/10.1038/s41586-023-06884-x

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Further information

- German Cancer Research Center (DKFZ), Heidelberg
- Heidelberg University, Center for molecular biology
- Hopp Children's Cancer Center Heidelberg (KiTZ)