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NEUROGENESIS

A striatal supply of new neurons

Frisén and colleagues recently showed that new neurons are born every day in the adult human hippocampus. In a follow-up study, the same research group now reports that neuroblasts are present in the human striatum throughout life, that they generate striatal neurons — mainly interneurons — and that newly generated striatal neurons are preferentially depleted in Huntington's disease.

It is well known that in rodents, adult neurogenesis occurs in the subventricular zone (SVZ) in the wall of the lateral ventricle, from where neuroblasts migrate to the olfactory bulb. The adult human SVZ also contains neuroblasts, but no neurogenesis has been detected in the human olfactory bulb. Frisén and colleagues therefore set out to establish whether SVZ neuroblasts might migrate elsewhere.

Transcriptome data, western blot analysis and immunohistochemistry of post-mortem human brain tissue revealed the expression of the neuroblast marker doublecortin (DCX) in the adult human striatum (as well as in the SVZ and hippocampus). DCX-expressing cells contained no or very little lipofuscin (an age pigment), suggesting that they were young cells. Importantly, in post-mortem tissue from patients with cancer who had received iododeoxyuridine (IdU) — which is incorporated into nuclear DNA during cell division — the authors detected IdU-labelled cells in the striatum (as well as in the hippocampus) that also expressed one or more neuronal markers. This indicates that the striatum contains not only neuroblasts but also newborn neurons.

The authors next made use of a birth-dating method that is based on the ^{14}C content of a cell's DNA, which is thought to reflect ^{14}C levels in the atmosphere at the time of the birth of the cell. Atmospheric ^{14}C levels peaked in the middle of the twentieth century (as a result of nuclear bomb tests) and declined after 1963; thus, the level of ^{14}C in DNA can be used as a relatively precise marker of a cell's birth date.

Application of this birth-dating method to nuclear DNA from human neurons from different brain areas revealed that for a minority of SVZ and striatum neurons, ^{14}C levels matched the ^{14}C levels that were present in the atmosphere after — rather than in — the individual's birth year, suggesting that these neurons were generated after the individual was born. This was not the case for cortical, cerebellar and olfactory bulb neurons. Computer modelling of the data showed that the best-fit model was one in which 25% of SVZ and striatal neurons showed turnover. The authors further showed that neuron turnover was restricted to striatal interneurons (which make up ~25% of striatal neurons) rather than medium spiny neurons. Non-neuronal cells in the striatum, including oligodendrocytes, also showed renewal.

Finally, the authors used the ^{14}C birth-dating method to show that the turnover rates for both neurons and oligodendrocytes were substantially lower in post-mortem striatum tissue from patients with Huntington's disease than in tissue from healthy controls. This suggests that newborn neurons are particularly vulnerable to the pathological processes associated with this disease.

Thus, humans show quite prominent neurogenesis in the striatum but none in the olfactory bulb. This contrasts with the pattern of prominent olfactory bulb neurogenesis and limited striatal neurogenesis in many other mammals. The functional role of newborn striatal neurons and the importance of their depletion in Huntington's disease are unclear, but they will be intriguing issues to explore in future research.

> "newborn neurons are particularly vulnerable to the pathological processes associated with [Huntington's] disease"

Leonie Welberg

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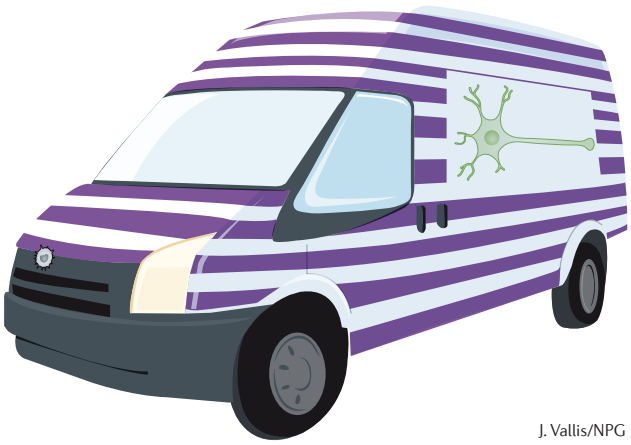

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