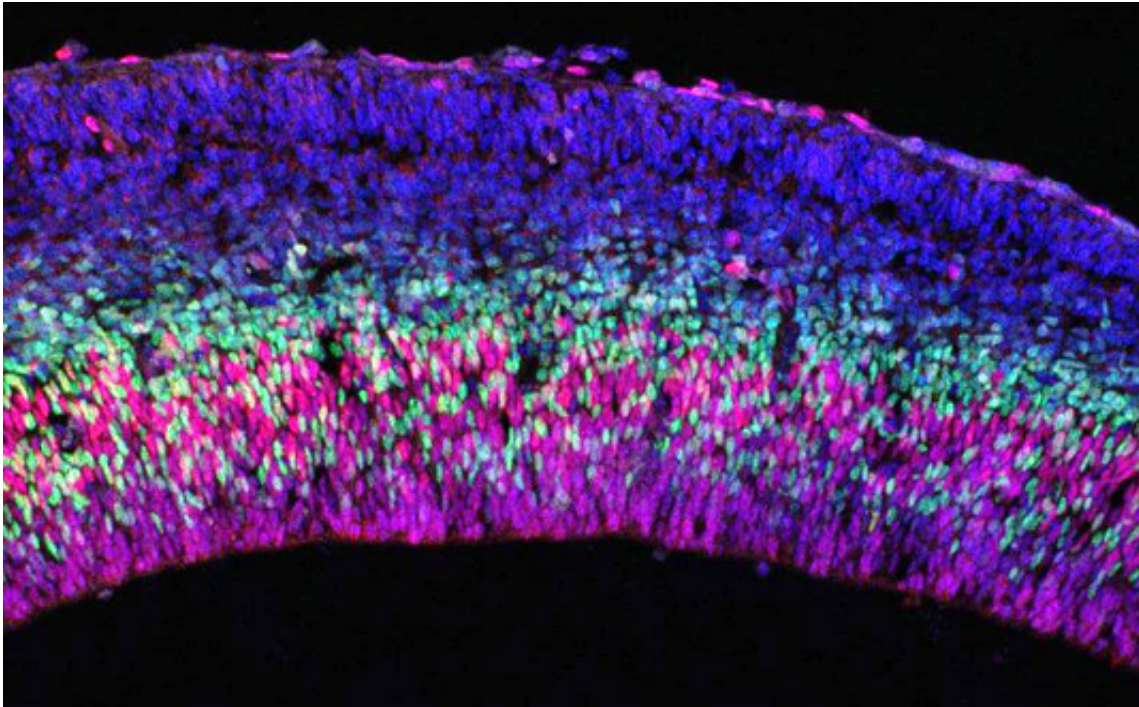


Epigenetics and neural cell death

October 26 2016



Cerebral cortex. Immunostained for Uhrf1 (neural stem cells, red). Credit: Vidya Ramesh

Ludwig-Maximilians-Universitaet researchers have demonstrated how deregulation of an epigenetic mechanism that is active only in the early phases of neurogenesis triggers the subsequent death of neural cells.

The generation of neurons from stem and progenitor cells is a complex, tightly regulated process known as neurogenesis. Researchers led by Professor Dr. Magdalena Götz, Chair of Physiological Genomics at

LMU and Director of the Institute for Stem Cell Research at the Helmholtz Zentrum München, have shown in collaboration with Professor Dr. Gunnar Schotta, Biomedical Center LMU, that epigenetic mechanisms which are brought into play at an early stage of neurogenesis, have an important impact on the subsequent fate of neurons. These new findings appear in *Genes and Development*, a leading journal in the field of developmental biology.

In order to elucidate the significance of early epigenetic modifications on the development of [neural cells](#) during embryogenesis in the mouse, Götz and her colleagues specifically inactivated the gene *Uhrf1*. This gene is known to control a number of epigenetic functions, including DNA methylation, and is active from very early stages of neurogenesis. The methylation of specific nucleotide bases in DNA often serves to switch genes off.

Conditional knockout of *Uhrf1*, in a region of the forebrain, led to the activation of endogenous retroviral elements (ERV) in the genome, which are otherwise silenced by methylation. Further investigation revealed that members of the Tet family of enzymes are largely mediating the demethylation of the ERVs, thus appearing to be functionally activated in the absence of *Uhrf1*. Moreover, these ERVs remained active not only in later stages of embryogenesis but also into postnatal stages, suggesting that their activation is non-reversible. The aberrant and ongoing activation of ERVs caused an accumulation of retroviral proteins in the affected cells and deregulation of genes and pathways. This in turn led to the progressive disruption of vital cellular processes and ultimately precipitated a massive wave of cell death.

"Our results reveal that certain key factors - such as the gene *Uhrf1* - that are transiently activated only in early [neurogenesis](#) can have a crucial impact on cell fate, which may only manifest weeks later," says Götz. "Our model system provides us with fascinating insights into these

mechanisms, which are also of great interest in the context of neurodegenerative diseases."

More information: Vidya Ramesh et al, Loss of Uhrf1 in neural stem cells leads to activation of retroviral elements and delayed neurodegeneration, *Genes & Development* (2016). [DOI: 10.1101/gad.284992.116](https://doi.org/10.1101/gad.284992.116)

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