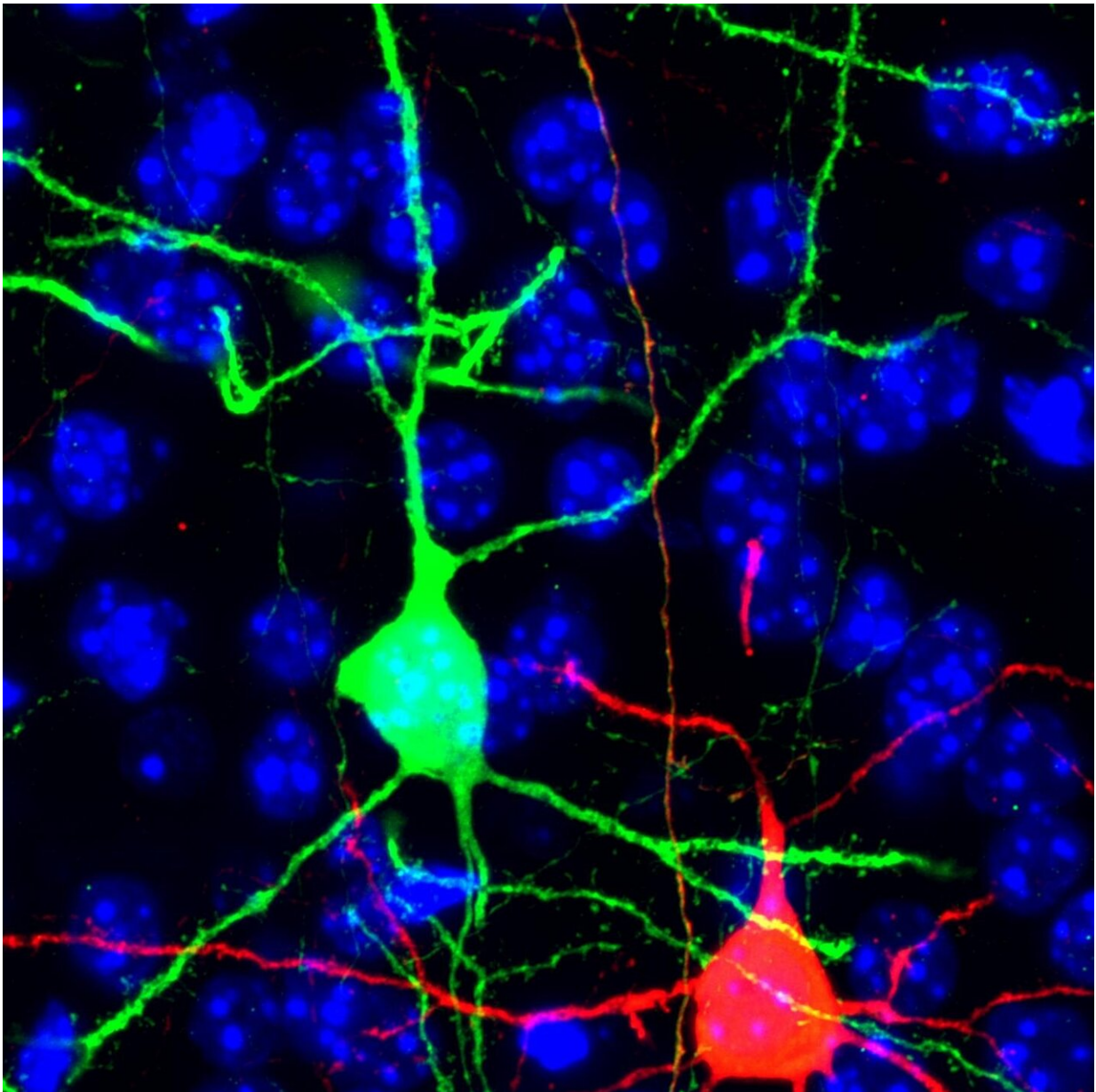


New function for potential tumor suppressor in brain development

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With the MADM technique, researchers can remove a gene from single cells and visualize what happens to these cells. Credit: IST Austria - Hippenmeyer group

The gene *Cdkn1c* could have been considered an open-and-shut case: Mice in which the gene is removed are larger and have bigger brains, so *Cdkn1c* should function to inhibit growth. This rationale has led to *Cdkn1c* being studied as a tumour suppressor gene. New research from the group of Simon Hippenmeyer, professor at the Institute of Science and Technology Austria (IST Austria), has now uncovered a novel, opposite role for *Cdkn1c*. When *Cdkn1c* is removed only in certain cells of the brain, these cells die, arguing for a new growth promoting role of *Cdkn1c*. The new research is published today in the journal *Nature Communications*.

Simon Hippenmeyer and his research group, including co-first authors Susanne Laukoter (Ph.D. student), Robert Beattie (postdoc) and Florian Pauler (senior technical assistant), removed *Cdkn1c* in a brain region called the [cerebral cortex](#) in mice and found a surprising result: Contrary to what had previously been thought, the cortex was smaller, not bigger, than in animals with a normal amount of *Cdkn1c*. To make sense of this seeming paradox, the researchers compared the effect of *Cdkn1c* loss in the whole animal with a loss of the gene in just a single tissue or even in [single cells](#) in the developing mouse.

Studying brain development and gene function at single cell level with MADM

Using a genetic technique called mosaic analysis with double markers (MADM) allowed the researchers to knockout a gene of interest in single cells and at the same time, visualize the effect of gene deletion on these cells under the microscope. When they removed the gene *Cdkn1c* in

cells in the whole cortex, the cortex was smaller. "When we take out the gene, cells die. In fact, we see massive death by apoptosis," Hippenmeyer explains.

In a cortex where *Cdkn1c* was removed, the researchers further modified single cells with MADM to observe their fate. They found that if a cell has two intact copies of *Cdkn1c*, the cell is protected against death. If a cell has just one intact copy of *Cdkn1c*, the cell dies. Intriguingly, it does not matter whether the DNA, the "[instruction manual](#)" in our cells that defines how products like proteins are made, is active and thus allows generation of proteins, or not. Just having two copies of the intact DNA, the intact instruction manual, is enough to protect a cell from death.

Implications for studies on brain malformations and tumour development

For Hippenmeyer, this study underlines the importance of studying both systemic effects of gene loss (i.e. gene loss in the whole animal) and the effect of gene loss in individual cells. "Our method reveals a new function of *Cdkn1c*, as taking the gene out in a single cell has a fundamentally different effect from taking it out in the whole animal. Systemic effects may mask the effect observed in individual cells. It is important to also study this in human conditions that lead to malformations of the brain, such as microcephaly."

As *Cdkn1c* and its role in the development of tumours has been studied extensively, the new research likely also has important implications for this field, says Florian Pauler. "There has been interest in *Cdkn1c* as it has been regarded as a tumour suppressor. Like the single [cells](#) and individual tissue we studied, tumours can also be seen as non-systemic. So, our findings change the way we should think about *Cdkn1c*, also in

tumours."

In the future, Hippenmeyer and his research group will continue to explore the mechanisms and functions of Cdkn1c. "When this piece of DNA is missing, something fundamental is changed and death is triggered in a cell. Of course, we want to now know why and how this happens," Hippenmeyer asserts.

More information: Susanne Laukoter et al, Imprinted Cdkn1c genomic locus cell-autonomously promotes cell survival in cerebral cortex development, *Nature Communications* (2020). [DOI: 10.1038/s41467-019-14077-2](https://doi.org/10.1038/s41467-019-14077-2)

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