Study reveals differences in DNA folding between neurons and other brain cells, links them to cell functions

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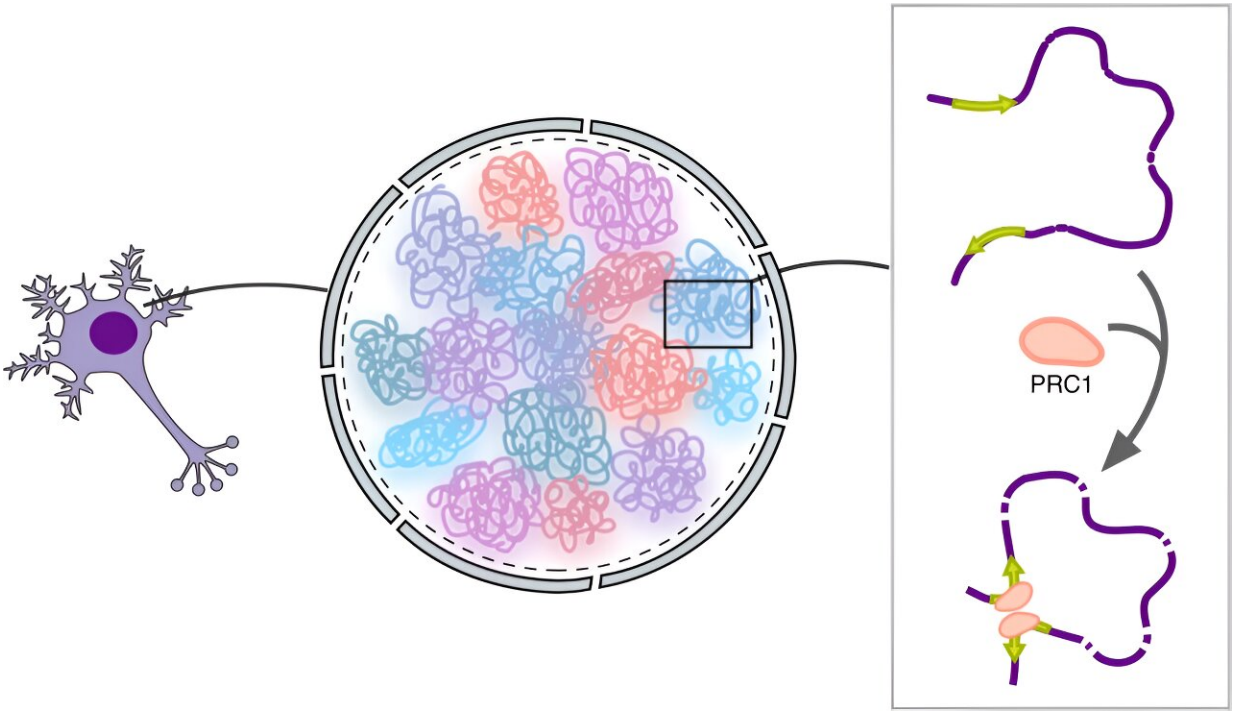

Left to right: a neuron, its nucleus, and repressive DNA contacts. Credit: Ilya Pletenev

Researchers from Skoltech and their colleagues have investigated nerve cell regulation. Mounting knowledge of regulation mechanisms could enable a better understanding of how the healthy brain operates and what goes wrong in developmental and oncological diseases associated with regulation errors. The study is published in the journal *Nucleic Acids Research*.

With a few exceptions, all the cells in an organism contain the same DNA. Despite this, even within one organ, there are cells of distinct types that vary widely in how they look and behave. The nervous tissue in the brain, for example, is composed of neurons, which transmit the signals, and the supporting glial cells.

Such specialization is the result of gene regulation, i.e., the selective activation and deactivation of the genes encoded in the DNA. It can occur both during a cell's initial development and in a mature cell.

One of the main mechanisms of gene regulation relies on three-dimensional structure. The way the several meters of DNA per cell nucleus are folded in 3D space makes it possible to switch certain genes on or off at a particular stage in the cell's life or for specific cell types.

Even among neurons, there are those of the excitatory and the somewhat rarer inhibitory variety, and these two breeds of nerve cells must run distinct genetic programs: They require different genes to be active. Appropriate DNA folding is a key mechanism that enables this.

The precise folding of DNA into 3D shapes is about building loops in all the right places. This is done by dedicated proteins that interact with certain genes essential for correct structure to emerge. If there's a problem with those genes, the cell misfolds its DNA, leading to

disrupted gene regulation, which can cause disease.

For example, an ill-regulated glial cell dividing way more often than it is supposed to is a cancer cell. Certain developmental disorders, too, are linked to incorrect spatial structure of DNA. One example is the Cornelia de Lange syndrome, a severe disease characterized by numerous physiological and cognitive abnormalities.

"Our research furthers our understanding of such diseases and of how gene regulation works in healthy cells," says Ilya Pletenev, the lead author of the study and a Skoltech Ph.D. student of life sciences.

"In this particular study, we demonstrated that the genes a neuron needs to be off tend to be close to one another in space, even though they might have been far away if you were to straighten out the DNA into a long one-dimensional strand. We think this probably makes it easier for repressor proteins to turn off those genes en masse.

"Also, we showed that the DNA of neurons and glial cells forms loops in different places. Moreover, it is the genes important for the cell type in question that tend to bunch up at the base of a loop, possibly making it easier for activator proteins to simultaneously switch them on."

More information: Ilya A Pletenev et al, Extensive long-range polycomb interactions and weak compartmentalization are hallmarks of human neuronal 3D genome, *Nucleic Acids Research* (2024). DOI: 10.1093/nar/gkae271

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