Gene expression in the nervous system: Researchers discover a mechanism for its targeted stimulation

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Dr. Vladyslava Gorbovytska, first author of the study, isolates RNA polymerase II from pig thymus. Credit: UBT / Chr. Wißler.

Genes are the carriers of our genetic information. They are read in our

cells and used to produce ribonucleic acids (RNAs). During this process, termed transcription, the enzyme RNA polymerase II has a decisive influence on the exact time at which genes are read and on the intensity with which this happens. In their recent *Nature Communications* article, researchers from the University of Bayreuth have shown exactly how RNA polymerase II is activated in nerve cells, and how this stimulates gene expression, the targeted use of genetic information. Their discoveries contain valuable starting points for further biomedical research.

The new research results were obtained in close cooperation between the Bayreuth research team led by Dr. Claus-D. Kuhn and partner universities in South Korea and Switzerland. In the jointly discovered mechanism the team found enhancer RNAs (eRNAs) to play a key role in activating RNA polymerase II—Pol II for short. Enhancer RNAs are non-coding, i.e. they are RNA molecules that are not used as blueprints for protein production. As the researchers were able to decipher, enhancer RNAs switch on the activity of Pol II. They do so by detaching NELF (Negative Elongation Factor), a large molecular complex bound to Pol II, from Pol II. NELF normally blocks Pol II activity by binding to it.

However, enhancer RNAs can only act as "liberators" of Pol II under two conditions: They need to have a minimum length and they need to be of a characteristic molecular composition. If both these conditions are met, multivalent interactions occur between the long enhancer RNAs and the NELF complex, as the Bayreuth researchers discovered. This means that enhancer RNAs simultaneously dock to a number of different binding sites that are distributed over several subunits of NELF. Only by means of these interactions are they able to detach NELF from Pol II. Enhancer RNAs thereby ensure that Pol II is reactivated and resumes the process of transcription following the NELF-induced paused state. "For the first time, we have succeeded in demonstrating a direct mechanistic

connection between enhancer RNAs and the transcription process controlled by Pol II, which is a key component of gene expression," says Dr. Claus-D. Kuhn, Heisenberg Professor for RNA Biochemistry at the University of Bayreuth.

The Bayreuth researchers and their cooperation partners gained their new insights by studying cortical neurons in mice. As soon as these neurons are stimulated by electrical stimuli, they produce large amounts of enhancer RNAs for a short period of time. These non-coding RNAs then activate genes that are important for nerve growth and their improved interconnectivity. They achieve this by detaching the NELF complex from Pol II. "To the best of our knowledge, this is the first time that a direct, mechanistic link between neuronal activity, enhancer transcription, and gene activation has been shown," says Bayreuth biochemist Dr. Vladyslava Gorbovytska, first author of the study. "In the future, the knowledge we have gained could make it possible to specifically modulate brain activity. This would be a significant asset for the treatment of many neurodegenerative diseases."

The study, published in *Nature Communications*, also expands previous knowledge regarding the role of enhancers, which are regulatory areas in DNA. Enhancers are known to be indispensable for initiating transcription in higher organisms, such as humans. This is the case as they serve as binding platforms for so-called transcription factors. The research conducted at the University of Bayreuth now shows that they influence gene expression in yet another, universally applicable way: Enhancers are read by Pol II, resulting in large amounts of enhancer RNAs. In this respect, these non-coding RNAs owe their existence precisely to the enzyme that they later release from a paused state and activate.

More information: Vladyslava Gorbovytska et al, Enhancer RNAs stimulate Pol II pause release by harnessing multivalent interactions to

NELF, *Nature Communications* (2022). DOI: 10.1038/s41467-022-29934-w