From gene expression to behavior – a novel role of SRF protein controlling gene expression in the regulation of social behavior. In the latest work published in the *Cellular and Molecular Life Sciences* scientists from the Center of Excellence for Neural Plasticity and Brain Disorders BRAINCITY from the Nencki Institute of the Polish Academy of Sciences have shown long term consequences of changes in early gene expression for future deficits in social interactions.

Doctor Matylda Roszkowska and Anna Krysiak, M.Sc. together with the research team working under the supervision of Professor Katarzyna Kalita showed a novel link between disturbances in the process of retrieving the information encoded in genes, and abnormal social behavior in the adulthood.

- Neurodevelopmental disorders such as Autism Spectrum Disorders, ADHD, or schizophrenia belong to the complex group of disorders characterized by cognitive impairments and social deficits. They are often caused by disturbances in gene expression programs in the developing nervous system – explains Dr. Roszkowska. Alterations in transcription impair gene function and affect protein synthesis. Such impairments may lead to changes in the number, structure, and function of synapses (specialized connections between neurons) – affecting neuroplasticity - one of the fundamental brain features.

- Moreover, it has to be stressed that synapse alterations are among the hallmarks of the neurodevelopmental disorders contributing to their clinical outcome. Among the typical disease symptoms are disturbances in social behavior including problems to establish complex interactions within species – describes Anna Krysiak.

Unraveling the neurobiological underpinnings underlying deficits in social behavior constitutes a challenge in contemporary neuroscience. The lack of appropriate tools and diagnostic tests allowing unbiased, accurate measurements of social behavior of animals living in the groups limits the studies looking for a possible link between impaired gene function, and animals' social interactions. Understanding the mechanisms responsible for neurodevelopmental deficits is crucial for effective therapeutic strategy – highlights Professor Kalita.

In order to study a relationship between changes in gene expression occurring at the early stages of the development, and future aberrations in animals' behavioral phenotype, scientists from the BRAINCITY have used genetically modified animals lacking one of the key proteins regulating gene activity in the brain – namely SRF (Serum Response Factor) transcription factor. Professor's Kalita's group took advantage of innovative system Eco – HAB® developed by Professor's Knapska group at the Nencki Institute. The system guarantees accurate, highly reproducible assessment of complex social interactions in mice without experimenter intervention during the tests.

Their research proved that lower SRF expression affects social phenotype of female and male mice. The animals exhibited social phobia symptoms, and avoided interactions with familiar conspecifics in the cage. The abnormal social behavior was accompanied by structural and functional changes of dendritic spines, which harbor the majority of excitatory synapses in the brain. In the *in vitro* experiments Dr. M. Roszkowska and A. Krysiak confirmed that silencing SRF expression during neuronal development disrupts excitatory neurotransmission. SRF-depleted neurons had significantly lower level of AMPA receptor subunits (AMPAR is

selectively activated by major brain neurotransmitter – glutamate). The aforementioned changes were accompanied by smaller number of functional synapses.

- Alterations in dendritic spine structure, namely, increased number of long, immature protrusions together with a smaller number of AMPA receptor subunits, indicate that SRF-dependent regulation of gene expression at the early stages of brain development modulates effective synapse maturations – explains Professor Kalita. The changes at the molecular level may constitute one of the mechanisms leading to neurodevelopmental disorders, together with their accompanying behavioral changes in the adulthood.

- Our research provides novel information valuable to understand the relationship between gene expression at critical periods during the development of the nervous system, and future neurobiological deficits symptomatic in different brain diseases – Professor Kalita concluded.

Professor Katarzyna Kalita was a laureate of the FNP Homing and Powroty programs.

The BRAINCITY Center was established within the framework of the International Research Agendas Programme (MAB) implemented by the Foundation for Polish Science since November 2015 under the Smart Growth Operational Programme.