DOI 10.18699/SBB-2022-127

Age-related alterations in the mouse liver circadian clock are caused by an imbalance of the NAD+ consumption system

Podkolodnyy N.L.[1, 2]*, Tverdokhleb N.N.[1], Podkolodnaya O.A.[1]

[1] *Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia*

[2] *Institute of Computational Mathematics and Mathematical Geophysics, SB RAS, Novosibirsk, Russia*

** pnl@bionet.nsc.ru*

Data on the role of NAD+-dependent histone deacetylase SIRT1 in the integration of circadian rhythm regulation and metabolic pathways, as well as on the function of NAD+ as a "metabolic oscillator" have opened a promising direction in this area. Especially important is the experimentally observed decrease in the cellular level of NAD+ in both chronological and biological aging in various tissues in experimental animals and humans. The liver is the main metabolic organ of mammals, providing de-novo NAD+ synthesis and NAD recycling. Therefore, the analysis of the interaction of the liver circadian clock with the NAD+ consumption system and the modeling of age-related changes associated with these interactions is the actual task.

A mathematical model of the interaction of the circadian oscillator in the mouse liver with the NAD+ consumption system, including the enzyme SIRT1, PARP1, CD38, whose activity changes with age, has been developed and tested on experimental data.

We included in our model the genes Arntl, Clock/Npas2, Per1/2, Cry1/2, Rorα/γ, Rev-Erbα/β, Dbp, Nfil3, Nampt, which are important for the functioning of the circadian oscillator in the mammalian liver (mouse). To verify the model, we used experimental data with various types of impacts, knowledge about the intervals of possible values of model parameters and the effect of knockout of various genes on the dynamics of the model and the oscillation period, the relationship between amplitudes, phases of model variables.

The simulation showed a pronounced circadian rhythm of the CB38, PARP1 and SIRT1 activity, and the fact that age-related changes in the activity of these enzymes lead to increased NAD+ catabolism and its depletion. Such disorders can be one of the causes of dysfunction of circadian oscillators in the liver and contribute to disruption of circadian rhythms in the body as a whole.

Acknowledgements: Supported by FWNR-2022-0020, and No. 0251-2021-0004.