Study on the aggregation of PHC3 protein in microbial and human cells

P-02.4-14

D.V. Kachkin[I,II,III], A.A. Zelinski[I,II], J.I. Khorolskaya[IV], K.Y. Kulichikhin[I], A.A. Rubel[I,II,III], Y.O. Chernoff[I,V]

[I]Laboratory of Amyloid Biology, St. Petersburg State University, St. Petersburg, Russia, [II]Department of Genetics and Biotechnology, St. Petersburg State University, St. Petersburg, Russia, [III]Sirius University of Science and Technology, Sochi, Russia, [IV]Institute of Cytology of the Russian Academy of Science, St. Petersburg, Russia, [V]School of Biological Sciences, Georgia Institute of Technology, Atlanta, Georgia, United States of America

Amyloids are insoluble highly ordered protein aggregates of a fibrillar nature, which are held together by intermolecular cross-beta sheets. The importance of amyloids is related to their role in a variety of human diseases, such as Alzheimer's, Huntington's and Parkinson's diseases, prion diseases and type II diabetes. Recent data also uncover the existence of functional amyloids in various organisms.

By using the yeast-based test system described previously (Chandramowlishwaran et al. 2018 J. Biol. Chem. 293: 3436), we have identified new amyloidogenic proteins in the human proteome. Among them, short isoforms of the human PHC3 protein were found, that demonstrate amyloid properties both in yeast cells and when produced in E. coli.

The full-length PHC3 protein is one of the key components of the polycomb complex (PcG), that is necessary for maintaining the repressed state of a variety of genes, including Hox-genes, during the development of an organism. The function of short isoforms of PHC3 remains unknown thus far.

We have shown that short isoforms of the PHC3 protein, fused with a fluorophore, form detergent-resistant aggregates during overproduction in HEK293T human cell culture. Using antibodies to the full-length PHC3 protein, we have demonstrated that full-length PHC3 is colocalized with the aggregated short isoforms.

We propose that aggregation of the short isoforms of the PHC3 protein can result in sequestration of its full-length isoform, altering the assembly and activity of the polycomb complex and leading to a change in the expression a variety of genes. Ongoing experiments are aimed at testing this model.

This work was performed with the support from RFBR grants 19-34-51054 and 19-34-90153, and from the SPbSU project 51140332, and with the technical help of the SPbSU Resource Centers “Chromas”, “Molecular and Cell Technologies” and “Biobank”.