Contribution ID: **1454** Type: **Oral**

Structural Analysis of Hybrid Ferritin Oligomers Using AlphaFold2 Predictions and their Potential Biomedical Applications

Tuesday, 31 October 2023 17:35 (15 minutes)

Ferritin is a protein complex whose presence is vital in almost all living organisms due to its responsible for storing iron. The protein is essential to iron homeostasis and is involved in a wide range of physiologic and pathologic processes. According to [1], ferritin's mechanism of self-assembly can be used as part of an effective small molecule delivery system. Therefore, there are a lot of potential application of ferritin in medicine and biotechnology, especially in vaccine production. We have studied some aspects of the process of ferritin's self-assembly using ColabFold v1.5.2 which is a tool based on Alphafold2. It is an artificial intelligence system that can predict three-dimensional structures of proteins from amino acid sequences with great accuracy [3]. AlphaFold2 has already proven its power to predict the three-dimensional structure of the majority of 200 million proteins [4], and recent research only confirms its importance for science [5,6].

In this work, we performed an analysis of different hybrid oligomers of ferritin and recombinant protein linked to ferritin. We examined ferritin from Helicobacter pylori, which is a globule of 24 identical subunits. Assuming that physical or chemical action could disrupt its structure into oligomers of fewer subunits, we wondered what configurations they could be formed into. Using AlphaFold2, dimers, trimers, and tetramers were obtained that demonstrate significant structural similarity to the arrangement that associations of the corresponding number of subunits have in the native state of the whole globule. Unexpected structures were also obtained - for example, a trimer with cylindrical symmetry. Next, given the potential of ferritin as a small molecule delivery vehicle, we investigated the possibility of assembling hybrid globules from ferritin subunits (Fer) and fusion proteins (FerS) that were constructed by linking a ferritin subunit with a small protein. Using Alphafold2 we obtained all possible variants for hybrid dimers, trimers and tetramers. We then compared their similarity with the corresponding regions in the structure of the native ferritin globule. We obtained structures that show topological similarity to the native ferritin globule for hybrid protein oligomers such as $Fer-FerS$, $(FerS)_2$, $(Fer)_2-FerS$, $Fer-(FerS)_2$, $(FerS)_3$, $(Fer)_3-FerS$, $Fer-(FerS)_3$, $(FerS)_4$. We were unable to obtain a corresponding structure for the oligomer composed of two original ferritin subunits and two subunits cross-linked with a small protein. The predicted structures differed significantly from the corresponding regions of the native globule.

From this we conclude that there is reason to believe that hybrid globules with attached small molecules could be produced in the future and used for drug delivery and other biomedical and scientific purposes. We will continue to explore oligomers from a larger number of monomers to improve our understanding of the ferritin-based globules self-assembly.

We acknowledge the support from the Russian Science Foundation (RSF) Project 22-74-00044.

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Session Classification: Life Science

Track Classification: Life Science