The ribosome: A new target for antiprion medicines

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New research results from Uppsala University, Sweden, show that the key to treating neurodegenerative prion diseases such as mad cow disease and Creutzfeldt-Jakob disease may lie in the ribosome, the protein synthesis machinery of the cell. The results were recently published in the *Journal of Biological Chemistry*.

Prion diseases are fatal neurodegenerative diseases caused by misfolding of prion proteins. Examples of prion diseases are scrapie in sheep, mad cow disease and Creutzfeldt-Jakob disease in human.

What triggers misfolding of the prion proteins to the amyloid disease form is an open question. The inadequate knowledge in the field about the factors involved in prion formation makes the discovery of effective medicines for prion diseases rather challenging.

"We have now shown that the protein folding activity of the ribosome (PFAR) is most likely involved in prion propagation and thus, can be a specific target for antiprion medicines. If we understand the mechanism fully, we will be able to find ways to stop that too.", says Suparna Sanyal, senior lecturer at the Department of Cell and Molecular Biology, Uppsala University .

The ribosome is the protein synthesis machinery of the cell. The mechanism of protein synthesis by the ribosome is well characterized, while PFAR is a rather recent discovery. PFAR is a ribosomal RNA dependent function of the large subunit of the ribosome irrespective of

its source. The PFAR center closely overlaps the peptidyl transferase center although the nucleobases responsible for these two functions are not all common.

"Our results show that two prion inhibitors 6-aminophenanthridine and guanabenz acetate implement antiprion activity by binding to ribosomal RNA and inhibiting PFAR. Thus, the ribosome and more specifically PFAR is the new target for antiprion medicines. Furthermore, we have developed an in vitro PFAR assay, which can be used as a platform for screening prion inhibitors in a high-throughput fashion. This assay is much more time and cost-effective than standard prion assays", says Suparna Sanyal.

More information: Pang, Y. et al. (2013) The antiprion compound 6-Aminophenanthridine inhibits protein folding activity of the ribosome by direct competition. *J. Biol. Chem*. doi/10.1074/jbc.M113.466748

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