New findings on protein misfolding

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Misfolded proteins can cause various neurodegenerative diseases such as spinocerebellar ataxias (SCAs) or Huntington's disease, which are characterized by a progressive loss of neurons in the brain. Researchers of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Germany, together with their colleagues of the Université Paris Diderot, Paris, France, have now identified 21 proteins that specifically bind to a protein called ataxin-1. Twelve of these proteins enhance the misfolding of ataxin-1 and thus promote the formation of harmful protein aggregate structures, whereas nine of them prevent the misfolding.

Proteins only function properly when the chains of amino acids, from which they are built, fold correctly. Misfolded proteins can be toxic for the cells and assemble into insoluble aggregates together with other proteins. Ataxin-1, the protein that the researchers have now investigated, is very prone to misfolding due to inherited gene defects that cause neurodegenerative diseases. The reason for this is that the amino acid glutamine is repeated in the amino acid chain of ataxin-1 very often - the more glutamine, the more toxic the protein. Approximately 40 repeats of glutamine are considered to be toxic for the cells.

Now, Dr. Spyros Petrakis, Dr. Miguel Andrade, Professor Erich Wanker and colleagues have identified 21 proteins that mainly interact with ataxin-1 and influence its folding or misfolding. Twelve of these proteins enhance the toxicity of ataxin-1 for the nerve cells, whereas nine of the identified proteins reduce its toxicity.

Furthermore, the researchers detected a common feature in the structure of those proteins that enhances toxicity and aggregation. It is a special structure scientists call "coiled-coil-domain" because it resembles a double twisted spiral or helix. Apparently this structure promotes aggregation, because proteins that interact with ataxin-1 and have this domain enhance the toxic effect of mutated ataxin-1. As the researchers said, this structure could be a potential target for therapy: "A careful analysis of the molecular details could help to discover drugs that suppress toxic processes."

More information: Identification of Human Proteins That Modify Misfolding and Proteotoxicity of Pathogenic Ataxin-1, *PLoS Genetics*, doi: 10.1371/journal.pgen.1002897

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