Proteins must fold into a specific shape to perform their function. When they don’t, the cell may be compromised. Protein misfolding is a potential contributor to neurodegenerative diseases, including ALS. Heather Durham, Ph.D., of the Montreal Neurologic Institute and McGill University, outlined the mechanisms cells have for controlling protein misfolding and described related therapeutic avenues being explored in ALS. She was the featured speaker at a recent webinar sponsored by The ALS Association.

A protein begins as a string of amino acids, whose sequence is determined by the gene that codes for the protein, Dr. Durham explained. The protein folds into a three-dimensional shape, with loops and folds and bumps, all determined by the amino acid sequence. Some proteins fold into their final shape spontaneously, but many others require the assistance of so-called chaperone proteins. Chaperones not only help with the initial folding, but can also re-fold proteins that become unfolded or misfolded. Stresses of many kinds, including heat, can cause such misfolding; the chaperones are also known as “heat-shock proteins.” Gene mutations change the amino acid sequence, and that also causes misfolding. Mutations in the SOD1 gene cause the SOD protein to misfold, for instance.

When a protein misfolds, not only does it lose its function, but it may gain a new toxic function. This is especially common when the misfolding exposes a region of the protein normally hidden on the interior. Such a region is likely to attract and stick to other proteins, leading them to misfold and creating large protein aggregates. The protein TDP-43 forms aggregates in virtually all people with ALS. “Amyloid” is a general name for many common types of protein aggregates, including those seen in ALS, Parkinson’s disease and Alzheimer’s disease. “These structures are often toxic,” Dr. Durham noted. “This is a common theme in neurodegenerative disorders.”

Toxicity may arise from disrupting processes at cell membranes, interfering with transport of other molecules or sequestering important proteins such as growth factors. If protein aggregates are released from the cell, they may trigger inflammation, which can harm neurons.

If chaperones cannot fix the misfolded protein, they can instead tag it for destruction through one of several recycling pathways. These include the proteasome and the lysosome. When these processes operate normally, small amounts of misfolded protein can be easily recycled. “All these different mechanisms cooperate and interact to keep the proteins of the cell functional,” Dr. Durham said. However, problems arise when there is either too much protein, too much of it forms aggregates, or the recycling processes are impaired. “Each step of this pathway can be compromised in neurons in various forms of ALS.” For instance, proteasome
activity is known to be reduced in the spinal cord and cerebellum (a region at the back of the brain) in both familial and sporadic ALS.

One potential therapeutic strategy is to increase the production of chaperones. To do that, Dr. Durham is exploring the mechanisms that regulate the activity of the genes that code for them. She has used so-called gene-specific “inducers” to increase that activity, a strategy that has shown some promise in cell culture but has proved difficult to translate into animal models. Another strategy uses a “co-inducer” to increase the efficiency of binding between gene and inducer. One co-inducer, arimoclomol, is currently in clinical trials in ALS.

“There may also be potential in some Chinese herbal medicines,” some of which appear to increase chaperone production as part of their effect. “What keeps us going is the possibility of finding a treatment,” Dr. Durham said.

Lucie Bruijn, PhD, Chief Scientist for The ALS Association and host of the webinar, noted that the commonalities among neurodegenerative diseases suggest that there are key pathways in all, including protein recycling, that may be valuable to exploit for therapy development. “Hopefully, clues from other diseases may be useful in understanding ALS as well,” she said.

To view the webinar in its entirety, visit https://alsa.webex.com/alsa/ldr.php?AT=pb&SP=MC&rID=68694987&rKey=c37a61c1d1d3dea2 .