**Alteration of protein citrullination and its effects on protein function in ALS**

In neurodegenerative diseases such as ALS, Alzheimer’s disease (AD), Parkinson’s disease (PD), and frontotemporal dementia (FTD), there are dramatic changes in post-translational modifications (PTMs) of proteins. PTMs are additions or removal of moieties on one or multiple amino acids in proteins. These modifications are catalyzed by enzymes after proteins are synthesized. For example, phosphorylation is catalyzed by a class of enzymes called kinases. It adds a phosphate group to specific amino acids. On the other hand, citrullination is catalyzed by peptidyl arginine deiminases (PADs), which remove the ketimine group from the amino acid arginine and replace it with a ketone group.

These modifications change charges at the modified amino acid positions. For example, phosphorylation adds negative charges, whereas citrullination removes positive charges. The charge changes can alter interactions between amino acids within the protein or interaction with other proteins, resulting in modulation of protein function.

In physiological conditions, cells conduct PTM to regulate protein functions to meet their needs in response to various functional requirements. In pathological conditions such as neurodegenerative diseases, cellular functions often go haywire, and PTMs become dysregulated. The dysregulation leads to a disconnection between cellular functional needs and PTM, causing some PTMs to become detrimental to the health and functioning of the cell.

PTMs have been intensely studied. For example, tau is a protein that forms toxic protein aggregates in AD. Tau is heavily phosphorylated to an abnormal degree both in the amount and the amino acid positions. Phosphorylation at some amino acids has been shown to increase protein aggregation and its toxicity to neurons. These research results have been used to design therapeutics targeting phosphorylated tau. In addition, phosphorylated tau has been used as a disease biomarker for diagnosing AD and evaluating AD progression in clinical trials.

Protein citrullination has also been shown to be increased in AD, PD, and other neurodegenerative conditions. However, whether similar changes occur in ALS is not known. Furthermore, how changes in protein citrullination affect the neurodegenerative process is also not understood. To answer these questions, Dr. Zuoshang Xu’s and Dr. Paul Thompson's labs at the Department of Biochemistry and Molecular Biotechnology, University of Massachusetts Chan Medical School, have joined forces and begun investigating protein citrullination in ALS.

They initiated their research in two mouse models for ALS. In their first publication from this research [1], They show that protein citrullination is increased dramatically in these mouse models. The increase is correlated temporally with the disease progression and spatially with the areas of neurodegeneration in the central nervous system (CNS), such as the spinal cord and the brainstem. Additionally, at the cellular level, there is a divergence between the neurons and glial cells. Whereas citrullination is dramatically increased in astroglia, it is decreased in neurons. Most strikingly, citrullinated proteins are almost exclusively accumulated in the protein aggregates, suggesting that citrullination may drive protein aggregation, thereby promoting disease progression.

Currently, they are conducting studies on human ALS samples to verify the findings from the mouse models. Their yet-to-be-published results indicate that similar changes in protein citrullination occur in human ALS. Their ongoing and future studies will determine which proteins are altered in citrullination and where on the proteins citrullination occurs and is changed in the disease. The knowledge gained will enable them to investigate further how the changes in protein citrullination impact ALS and whether alterations in protein citrullination in the disease can be used as biomarkers for ALS diagnosis and clinical trials.

1 Yusuf IO, Qiao T, Parsi S, Tilvawala R, Thompson PR, Xu Z (2022) Protein citrullination marks myelin protein aggregation and disease progression in mouse ALS models. Acta Neuropathol Commun 10: 135 Doi 10.1186/s40478-022-01433-5