Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that causes degeneration of upper and lower motor neurons, resulting in muscle weakness and eventual death within 2-5 years after diagnosis. Motor neurons in more than 90% of the ALS patients contain TAR DNA binding protein-43 (TDP-43) aggregation which is thought to be critical for ALS pathogenesis. However, the molecular mechanism by which this aggregate is formed remains poorly understood.

The gene for valosin-containing protein (VCP), an AAA+ ATPase that unfolds and segregates client proteins from macromolecular complexes or membranes, is mutated in ALS patients. Some of these mutations are demonstrated to alter ATPase activity of VCP. However, how the ATPase activity of VCP contributes to ALS pathogenesis was largely unknown. Here we confirmed that TDP-43 aggregation is formed upon cellular stress conferred by hydrogen peroxide. Treatment of specific VCP inhibitor NMS-873 was found to suppress hydrogen peroxide-induced TDP-43 aggregation without affecting TDP-43 clearance. These results indicate that the ATPase activity of VCP is required for TDP-43 aggregation which is enhanced by ALS-derived mutation in VCP, and thereby VCP ATPase inhibitor such as NMS-873 is a potential therapeutic reagent for ALS patients.