

Targeting Proteinopathies: Understanding and Mitigating the Effects of Pathogenic Mutations in Cullin-RING Ligase Receptor

Abstract

The human body relies on intricate systems to remove malfunctioning proteins. When these systems fail, it can lead to the accumulation of harmful protein clumps, causing various diseases. In our recent research, we discovered a new mutation in a critical region of a protein acting as a cullin-RING ligase receptor. This mutation is linked to severe neurodevelopmental disorders, affecting a key part of the protein responsible for recognizing and tagging other proteins for removal. However, the exact way it causes disease is still unclear.

Our first goal is to understand which proteins are affected by this mutation. We will use a novel technique to identify these proteins and see how their stability or degradation is altered. Advanced imaging and biochemical methods will help us examine how the mutation disrupts interactions between the cullin-RING ligase receptor and its substrates (targets), focusing on those involved in brain function.

We have also created a model using a nematode species – *C. elegans*, which mimics the human mutation. These worms show symptoms like poor movement and excessive release of a neurotransmitters, similar to those seen in patients. Our second goal is thus to extend our research and create a unique *C. elegans* model that will allow us to identify substrates specific to the worm analog of the affected human protein. By targeting these pathways with genetic and drug interventions, we aim to understand the changes in neurotransmitter release observed in our animal model.

Since the mutation likely disrupts how the cullin-RING ligase receptor recognizes its targets, we will explore small molecules that can stabilize these interactions. We will start by modeling the structure of the affected protein with one of its known substrates. Using high-throughput virtual screening, we will search for small molecules that can enhance these interactions. Successful candidates will then be experimentally tested for further optimization and potential therapeutic use.

We expect to identify the direct targets of the cullin-RING ligase receptor and understand how the mutation leads to disease. This will provide insights into the molecular mechanisms underlying neurodevelopmental disorders. Our ultimate goal is to pave the way for developing new therapies that can restore normal protein degradation pathways or be used in targeted treatments. By combining clinical genetics, protein biochemistry, and innovative therapeutic strategies, our work aims to advance research into protein-related diseases and offer hope for novel treatments.