Evolutionary and Structural Basis of the EEVD-Dependent Mechanism of Amyloid Disaggregation driven by J-Proteins

Amyloid diseases, like Alzheimer's and Parkinson's, happen when the cell's natural systems for maintaining healthy proteins fail. A group of proteins called J-domain proteins (JDPs) play an important role in helping to break down these harmful protein clumps. This project aims to understand how certain types of these proteins, called human class B JDPs, evolved and how they work at a molecular level to remove amyloid plaques.

There are different types of JDPs. Class A JDPs are complex proteins, with several different parts, but they cannot break down amyloid fibers. They have a special structure called a zinc finger. Class B JDPs lack this zinc finger and instead rely on a specific part of another protein called Hsp70 to do their job.

This research aims to answer two key questions: First, how did the ability to break down amyloid fibers evolve? What changes in their structure allowed this new function? Second, how does a specific part of Hsp70, called the EEVD motif, activate class B JDPs to help remove amyloid fibers? The scientists believe that class B JDPs normally exist in a "restrained" state, where their activity is blocked. When the EEVD part of Hsp70 binds to them, it causes a change in shape that releases this block and activates the protein, allowing it to work on amyloid fibers.

To study this, scientists will look at the evolution of these proteins over time, using methods from genetics and biochemistry. They have already found evidence that class B JDPs came from class A proteins a long time ago and gained the ability to break down amyloid fibers after losing their zinc finger. They will identify the specific mutations responsible for this change.

The team will also use advanced imaging methods to look at the structure of these proteins in their inactive (restrained) form and after activation. They will use computer simulations to understand how the shape of the proteins changes when the EEVD part binds. Some early experiments suggest that DNAJB1, a type of class B JDP, can exist in a closed, inactive shape, but binding of EEVD can change that.

By understanding these mechanisms, this project will help reveal how new protein activities evolve and how cells keep proteins healthy, which is crucial for tackling neurodegenerative diseases.