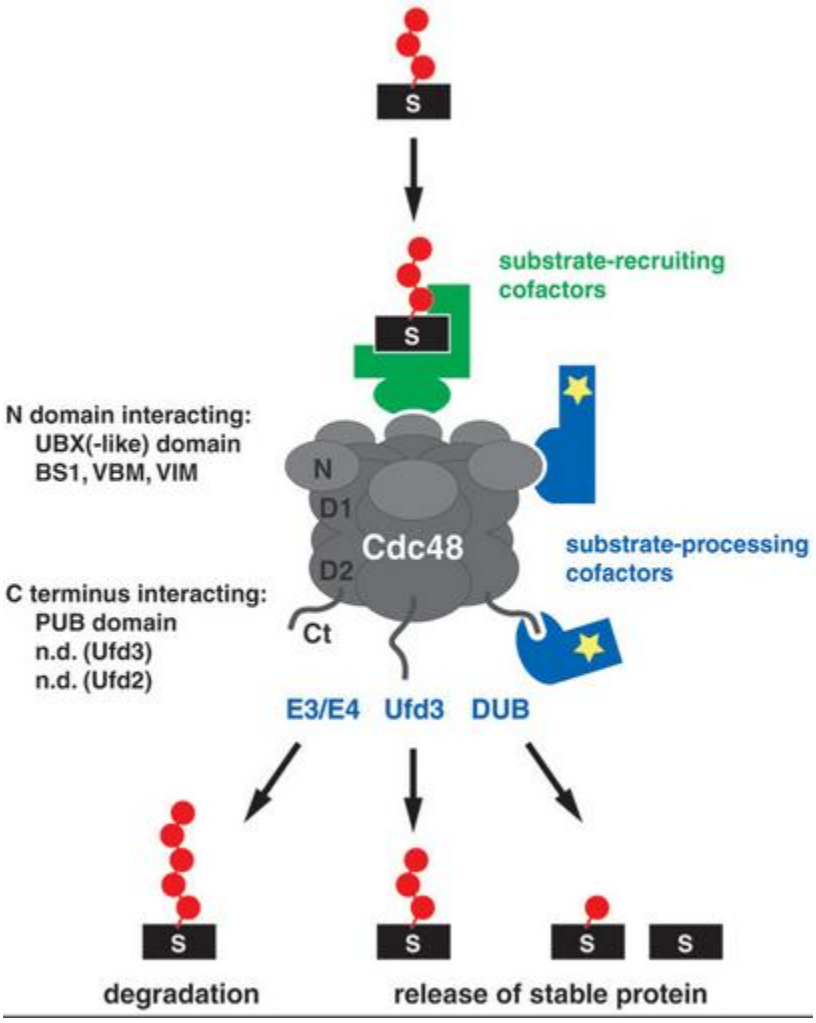
Overview

Cdc48 is a hexamer protein that belongs to a group of enzyme called ATPase. Past research has shown that it helps to control the quality of protein activities such as: endoplasmic reticulum associated protein degradation (ERAD), transcriptional and metabolic regulation, DNA damage response, and many more. New research shows that Cdc48 regulates the degradation of damaged proteins by helping to store them in aggresome when the cell is under stress and later to destroy the damaged proteins.



Structure

Cdc48 is a hexamer protein. It has central core with six protomers attached to it to form a ring. The four domains that make up a protomers an amine terminus, AAA region (D1 and D2), and a carboxyl tail. There are twelve ATPase active sites for ATP hydrolysis reaction. When a hydrolysis reaction occurs, Cdc48 changes its shape by maneuvering the six protomers that allows for the opening and closing of the rings. Furthermore, different temperatures allows for different parts of the domain to be more activity than others. For example, D1domain works at its maximum at the 60˚C while D2 domain works better at 37˚C. In addition, the conformation

change is necessary because it affects the function of the protein. If the protein does not work, it can result in a cell death. Furthermore, the carboxyl tail can be phosphorylated and acetylated that will affect the protein's ATPase activity, localization, and binding ability.

Function

The function of Cdc48 depends heavily on its cofactor. Each cofactor programs that protein to perform a specific function. Meanwhile, the substrate-processing factor will bind to the protein to direct the protein's path. One of the best known functions of the protein is in endoplasmic reticulum-associated protein degradation. Cdc49 forms a complex with Udf1 and Np14, which then bind to an ERAD ubiquitylated substrate. Consequently, this action causes a chain reaction that leads to the damaged proteins to be degraded in the proteasome. Another role that Cdc48 takes part in is mitochondrial protein degradation. Here, Vms1 replaces Ufd1 to form a complex with Cdc48. When cells are exposed to rapamycin or hydrogen peroxide, this activates the Cdc48 to be moved to the mitochondrial membrane to degrade selected mitochondrial proteins in a process called UPS. New research showed that a protein called E3 ligase Parkin and Cdc48 help to prevent damaged mitochondrial proteins from fusing with healthy ones. Cdc49 also plays a role in cytoplasmic protein degradation. Similar to ERAD, Cdc48 form the same complex. However, its role differs by removing the ubiquitylated enzymes from the glucose-induced degradation deficient (Gid) complex to create loose ends so that the damaged proteins can go into the proteasome to be degraded. In the nucleas protein degradation, Cdc48 complex helps to unfold and disassemble defected proteins with of its cofactors Ubx4 and Ubx5. Ribophagy is another process that depends on Cdc48. Here, mature ribosomes are degraded to make sure that the cell can survive. Cdc49 pairs up with Ubp3 and Bre5 to deubiquitylate the ribosome.

Works Cited

Buchberger, Alexander, Hilt, Wolfgang, Stolz, Alexandra, Wolf H. Dieter. "Cdc48: a power machine in protein degradation". *Trends in Biochemical Sciences*. October 2011.