Researchers identify a scaffold regulating protein disposal

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How does a cell manage to identify and degrade the diverse types of defective proteins and thus protect the body against serious diseases? The researchers Sabine C. Horn, Professor Thomas Sommer, Professor Udo Heinemann and Dr. Ernst Jarosch of the Max Delbrück Center for Molecular Medicine (MDC) Berlin-Buch, Germany, have now found a crucial piece in this puzzle. In an enzyme complex that plays a critical role in the quality control of proteins, they discovered a scaffold regulating the identification and disposal of various defectively produced proteins.

Proteins are the building materials and the machinery of life. They are found by the thousands in a cell and carry out vital tasks in the organism.

The production site of many of the proteins is located in a cell organelle called the endoplasmic reticulum (ER). Here the proteins are produced, folded and routed to their destination.

However, during protein production errors can occur: during the process proteins can be folded in the wrong way. Older proteins may also accumulate defects due to environmental stress.

They can lose their original structure and thus fail to carry out their function and may possibly even cause damage. Diseases can develop such as Alzheimer's, Parkinson's or cystic fibrosis. Defective proteins must therefore be detected in the cell and disposed of.

Protein quality control: rejects receive a molecular tag

Proteins run through a quality control process in the cell. For the identification of defective proteins, an enzyme complex - the HRD-ubiquitin ligase - plays a key role.

It functions like a kind of tagging machine: If it recognizes the protein as defective, it tags it with a molecule, the protein ubiquitin, thus marking it for disposal.

Great demands are placed on the HRD-ubiquitin ligase, because proteins adapt to their cellular locations and functions and thus have quite different structures.

For instance, there are water-soluble proteins inside the cell as well as water-insoluble proteins that are situated on or in the cell membrane.

Until now it remained unclear how the enzyme complex manages to recognize and mark such different types of proteins.

Flexible scaffold makes tagging machine universally usable

The study of the MDC researchers has now shed light on this puzzle. The researchers have discovered the central and flexible scaffold of the enzyme complex, the subunit Usa1. Depending on what is required, it tethers specific modules of the complex, connecting them with each other.

When identifying and tagging soluble proteins, Usa1 establishes the contact between the subunits Der1 and Hrd1.

Furthermore, the researchers discovered that the HRD-ubiquitin ligase binds with other HRD-ubiquitin ligases to form a larger enzyme complex in order to degrade insoluble membrane proteins. This process is also regulated by the subunit Usa1.

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