Ubiquitin

Ubiquitin is a small (8.5 kDa) regulatory protein that has been found in almost all tissues (ubiquitously) of eukaryotic organisms. It was discovered in 1975 by Gideon Goldstein and further characterized throughout the 1970s and 1980s.

They play a crucial role in the regulation of protein degradation and other cellular processes. It is a highly conserved protein, meaning it is structurally similar across a wide range of species, from yeast to humans. Ubiquitin functions as a molecular tag or marker, marking specific proteins for degradation, recycling, or other cellular activities.

The key functions of ubiquitin include:

Protein Degradation: The primary function of ubiquitin is to mark specific proteins for degradation by the proteasome, a cellular structure responsible for breaking down unwanted or damaged proteins. This process is critical for maintaining cellular health and regulating the levels of various proteins within the cell.

Protein Recycling: Ubiquitin also plays a role in protein recycling. When a protein is tagged with ubiquitin and degraded, the ubiquitin molecules are released and can be reused to tag other proteins. This recycling ensures a constant supply of ubiquitin for cellular processes.

Regulation of Protein Function: In some cases, ubiquitination can regulate the activity or localization of proteins without leading to their degradation. This process can affect various cellular functions, including signal transduction and DNA repair.

The process of attaching ubiquitin molecules to target proteins is called ubiquitination. It involves a coordinated series of enzymatic reactions carried out by three main types of enzymes:

E1 (Ubiquitin-activating enzymes): E1 enzymes activate ubiquitin by attaching it to a cysteine residue in the E1 enzyme.

E2 (Ubiquitin-conjugating enzymes): E2 enzymes transfer activated ubiquitin from E1 to the target protein with the help of an E3 ligase.

E3 (Ubiquitin ligases): E3 ligases are responsible for recognizing specific target proteins and facilitating the transfer of ubiquitin from the E2 enzyme to the target protein.

Ubiquitin can be attached to target proteins as a single molecule or in the form of polyubiquitin chains, where multiple ubiquitin molecules are linked together. Different types of ubiquitin chains, such as K48-linked or K63-linked chains, can have distinct effects on the fate of the target protein, determining whether it is degraded, undergoes a change in function, or is involved in other cellular processes.

The ubiquitin-proteasome system, which involves the ubiquitination and subsequent degradation of proteins, is a fundamental process in cellular biology and is essential for maintaining cellular homeostasis, responding to stress, regulating cell cycle progression, and more. Dysregulation of the ubiquitin-proteasome system is implicated in various diseases, including cancer and neurodegenerative disorders.

There are four genes in the human genome that produce ubiquitin: UBB, UBC, UBA52, and RPS27A.

The addition of ubiquitin to a substrate protein is called ubiquitination or ubiquitylation. Ubiquitination can affect proteins in many ways: it can signal their degradation via the proteasome, alter their cellular location, affect their activity, and promote or prevent protein interactions.

Ubiquitination is carried out in three main steps: activation, conjugation, and ligation, performed by ubiquitin-activating enzymes (E1s), ubiquitin-conjugating enzymes (E2s), and ubiquitin ligases (E3s), respectively. The result of this sequential cascade binds ubiquitin to lysine residues on the protein substrate via an isopeptide bond, cysteine residues through a thioester bond, serine and threonine residues through an ester bond, or the amino group of the protein's N-terminus via a peptide bond.

Blood ubiquitin C-terminal hydrolase (UCH-L1) and GFAP are increased early after stroke and distinct biomarker-specific release profiles are associated with stroke characteristics and type. Ren et al confirmed the potential of GFAP as a tool for early rule-in of ICH, while UCH-L1 was not clinically useful [1].

Ubiquitin-proteasome system

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Ren C, Kobeissy F, Alawieh A, Li N, Li N, Zibara K, Zoltewicz S, Guingab-Cagmat J, Larner SF, Ding Y, Hayes RL, Ji X, Mondello S. Assessment of Serum UCH-L1 and GFAP in Acute Stroke Patients. Sci Rep. 2016 Apr 14;6:24588. doi: 10.1038/srep24588. PubMed PMID: 27074724; PubMed Central PMCID: PMC4830936.