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MECHANISM OF ACTION OF UBIQUITIN PROTEIN AND ITS SIGNIFICANCE IN ORGANISMS

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Annotation: Ubiquitin is the founding member of a family of structurally conserved proteins that regulate a host of processes in eukaryotic cells. Ubiquitin and its relatives carry out their functions through covalent attachment to other cellular proteins, thereby changing the stability, localization, or activity of the target protein. This article reviews the basic biochemistry of these protein conjugation reactions, focusing on ubiquitin itself and emphasizing recent insights into mechanism and specificity.

Key words: Ubiquitination, organism, protein, DNA, N-terminus, mutation,

Ubiquitination (also known as ubiquitylation) is a form of post-translation modification (PTM) in which ubiquitin is attached to a target protein. Ubiquitin is a 76 amino acid protein that exists in the free form or can be conjugated to a protein as a single ubiquitin (i.e., monoubiquitination) or as a multiple ubiquitin (i.e., polyubiquitination). Ubiquitination plays versatile roles in protein functions ranging from protein degradation to subcellular localization and kinase activation. Three enzymes are involved in the ubiquitination pathway: Ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin-protein ligase (E3). Ubiquitination is highly relevant to the pathobiology of many human diseases. This review will explore the fundamentals of ubiquitination, its function, pathophysiology, and clinical significance of ubiquitination.[1]

Ubiquitination is a three-step process involving three enzymes: ubiquitin-activating enzyme (E1), ubiquitin-conjugating enzyme (E2), and ubiquitin-protein ligase (E3). E1 activates ubiquitin in an ATP-dependent manner, enabling its transfer onto the ubiquitin carrier enzyme, E2. Activated ubiquitin is then transferred by the ubiquitin protein ligase, E3, to a substrate protein. Monoubiquitination acts as a signal for nonproteolytic events such as endocytosis, histone regulation, DNA repair, virus budding, and nuclear export. Ubiquitin can also be attached to a target protein in polyubiquitination, where multiple ubiquitin molecules are attached to a single lysine (Lys) residue. Ubiquitin contains seven different lysine residues that can potentially be used for ubiquitin-chain extension.

The ubiquitin-proteasome is a well-studied pathway known to play a significant role in regulating protein homeostasis and trafficking. Ubiquitination regulates various cellular processes, including immune response, angiogenesis, cell proliferation, apoptosis, and DNA repair.

- Any given protein could be ubiquitinated at multiple sites with a different effect on the target protein. Targeting a specific ubiquitination site is proven to be challenging.
- Although various drugs (e.g., bortezomib) have been developed to inhibit the proteasome pathway, however, due to their non-specific activities, their therapeutic applications are limited.
- E3 ligases often have multiple substrates with diverse functions. Inhibiting an E3 ligase may prevent

the ubiquitination of other proteins that are not of point of interest, resulting in an unintended or off-target effect.

Although targeting protein ubiquitination has proven to be challenging, as we learn more about the ubiquitination pathway, new therapeutic strategies are expected to emerge .[3] Ubiquitination is a tightly regulated, highly specific, and ATP-dependent biological process carried out by a complex cascade of enzymes. Ubiquitination is an essential player in protein homeostasis, serving to rapidly remove unwanted or damaged proteins. The ubiquitination pathway is involved in the regulation of many basic cellular processes, including cell division and differentiation, response to environmental stress, cell differentiation, immune response, DNA repair, and apoptosis.[4] Ubiquitin is an evolutionarily conserved protein found in nearly all eukaryotic organisms. It is highly conserved and virtually identical across all life forms, whether human, yeast, or plant. Ubiquitin is a 76 amino acid protein. The main features of ubiquitin are its seven lysine (Lys) residues and the N-terminus. Ubiquitin can be ubiquitinated on any of the seven Lys residues or on the N-terminus. Lys48- and Lys63-linked chains are the most common polyubiquitination sites, which could lead to protein degradation and endocytosis, respectively.[3] Ubiquitination plays a crucial role in virtually every aspect of cellular functions. One of the best understood functions of ubiquitination is protein degradation. This pathway targets proteins to the proteasome, which degrades and recycles the proteins. As noted previously, it has a wide range of functions, including cell signaling, apoptosis, protein processing, immune response, and DNA repair.

These types of ubiquitination reactions act as a signal for endocytosis and transporting of cellular vesicles to lysosomes. Disruptions in this pathway have implications in many oncogenic formations. Ubiquitination of membrane protein trafficking has also shown associations with various viruses, such as Ebola and HIV, that make their way to the cell surface after replicating within the cell.[5]

Ubiquitination ultimately breaks down into three essential steps that are catalyzed by the enzymes ubiquitin-activating enzymes (E1), ubiquitin-conjugating enzymes (E2), and ubiquitin ligases (E3). The three steps are:

1. Activation: Ubiquitin-activating enzyme E1 uses an ATP-dependent process to establish a thioester bond between the C-terminal carboxyl group of ubiquitin and the cysteine group of the ubiquitin-activating enzyme.

2. Conjugation: The E2 ubiquitin-conjugating enzyme then binds to both the activated ubiquitin and E1 enzyme complex. E2 catalyzes the transfer of ubiquitin from the E1 site to the active site on E2 by way of a transesterification reaction.

3. Ligation: In the final step of the ubiquitination pathway, E3 ubiquitination ligase creates an isopeptide bond with the lysine of the target protein and the C-terminal glycine of ubiquitin.

The result is the formation of a ubiquitin-substrate complex.[2]. Like other PTMs, such as phosphorylation, the ubiquitination reaction is reversible. This is accomplished through the action of deubiquitinating enzymes (DUBs).[12] Identifying the E3 ligases substrate is critical to understand their implications in human malignancies and other diseases. Deregulation of E3-substrate interactions is often an indicator of many of these pathologies. Various assays were developed to identify the substrates of E3 ligases, such as shRNA- or CRISPR-Cas9-mediated screening and in vitro ubiquitination assay. Also, a genome-wide screening strategy called Global Protein Stability (GPS) profiling was recently developed to identify the previously unknown substrates of the E3 ligases. The GPS system made use of reporter proteins fused with hundreds of potential substrates independently. By inhibiting the ligase activity (causing ubiquitination not to occur), increased reporter activity shows that the identified substrates are accumulating. These results demonstrate the potential of these technologies as basic platforms for the global discovery of E3-substrate regulatory networks.[6]

As discussed in previous sections, the ubiquitin-proteasome pathway plays an important role in maintaining protein homeostasis and trafficking. Ubiquitination occurs throughout eukaryotic cell signaling and has been implicated in many malignancies through the gain of function and loss of function mutations.

Loss of function mutation on the tumor suppressor gene can lead to inhibition or activation of ubiquitination. The gain of function mutations has mainly been implicated with increased activation of ubiquitination. In von-Hippel Lindau (VHL) disease, the loss of function mutation in the VHL tumor suppressor results in hemangioblastoma formation in multiple organs, renal cell carcinoma, and pheochromocytoma—the VHL tumor suppressor gene codes for the VHL protein. The VHL protein is a type of E3 ubiquitin ligase that catalyzes the ubiquitination of hypoxia-inducible transcription factor-alpha (HIF1-alpha). HIF-alpha regulates erythropoietin (EPO) production and vascular endothelial growth factor (VEGF). Under normal physiologic conditions, HIF1-alpha remains hydroxylated. In the hydroxylated form, it can be recognized and degraded by the VHL protein. This results in the prevention of EPO and VEGF induction under normoxic conditions. In VHL disease, the gene mutation results in the VHL protein's inability to bind HIF-alpha, leading to uncontrolled growth. Another way ubiquitination has been implicated in malignancy is by how uncontrolled proliferation has been able to evade the ubiquitin-proteasome protein degradation pathway. The ubiquitin-proteasome system plays a vital role in colorectal cells in regulating the APC (adenomatous polyposis coli)/beta-catenin signaling pathway, which regulates the growth of colorectal epithelial cells. Mutations in APC result in the failure in the degradation of beta-catenin, which results in inhibited cell proliferation.

Ubiquitination also correlates with several genetic disorders. Angelman syndrome is a rare genetic disorder affecting the nervous system that results from a mutation in UBE3A, which codes for an E3 ubiquitin ligase. Previous genetic studies have proposed that the UBE3A-encoded E3 ubiquitin ligase is important for normal human cognitive function. 3-M syndrome is a disorder characterized by intrauterine growth retardation that results from mutations in CUL7, which is important in assembling an E3 ubiquitin ligase complex and promoting ubiquitination. Disruption of this pathway plays a role in the pathogenesis of 3-M syndrome.[8]

As discussed in previous sections, the ubiquitin-proteasome pathway plays an important role in maintaining cell homeostasis. Changes in this process can lead to the formation of tumors and neurodegenerative disorders. Thus, pharmacological treatments targeted at the ubiquitin-proteasome pathway provide potential opportunities to treat tumors and neurodegenerative disorders. For example, the ubiquitin ligase MDM2 plays an essential role in regulating P53 stability, and research is focusing on developing an inhibitor that disrupts this interaction. However, creating therapeutic targets against a specific ubiquitination enzyme is challenging because multiple ubiquitin E3 ligases ubiquitinate one protein, and targeting one enzyme may not be adequate. Proteasome inhibition is the only validated therapeutic target of the ubiquitin system. Bortezomib, a proteasome inhibitor, was approved in 2003 by the FDA to treat relapsing and refractory multiple myeloma.

Ubiquitin immunohistochemistry has played a crucial role in understanding the pathophysiology of neurodegenerative diseases and aiding in diagnosing these disorders. Inclusions (protein aggregates) containing ubiquitinated proteins are present in Alzheimer's disease, amyotrophic lateral sclerosis, and Parkinson's disea.

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