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Review

Proteostasis and neurodegeneration: The roles of proteasomal degradation and autophagy☆

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ABSTRACT

All proteins in a cell continuously turn over, each at its own rate, contributing to a cell's development, differentiation, or aging. Of course, unnecessary protein(s), or those synthesized in excess, that hamper cellular homeostasis should be discarded rapidly. Furthermore, cells that have been subjected to various environmental stresses, *e.g.*, reactive oxygen species (ROS) and UV irradiation, may incur various types of protein damage, which vitiate normal and homeostatic functions in the cell. Thereby, the prompt elimination of impaired proteins is essential for cell viability. This housekeeping is accomplished by two major catabolic routes—proteasomal digestion and autophagy. Strict maintenance of proteostasis is particularly important in non-proliferative cells, especially neurons, and it is plausible that its failure leads to a number of the neurodegenerative diseases becoming prominent in the growing elderly population. This article is part of a Special Issue entitled: Ubiquitin–Proteasome System.

1. Introduction

Proteins within a cell exist in a dynamic state, a balance between synthesis and degradation, in which they turn over continuously and perhaps stochastically. Indeed, the half-life of an individual protein ranges from minutes to months, a ~100,000-fold difference in timespan. Proteolysis plays a central role in protein renewal, which maintains the quality of proteins within the cell by destroying dysfunctional components. Two main sophisticated machineries—the proteasome and autophagy—ensure proteolysis in eukaryotic cells (Fig. 1). The proteasome, in collaboration with a refined ubiquitin system used for tagging target proteins, selectively degrades short-lived regulatory proteins involved in the homeostatic control of the cell, and abnormal proteins with aberrant structures, the excess accumulation of which is usually harmful [1]. By contrast, the lysosomal proteolysis guided by autophagy was initially thought to be a bulk protein degradation system designed to non-selectively engulf cytoplasmic constituents [2]. This latter route was seen to be a way for the cell to secure nutrients while under starvation conditions. However, more recently, surprising data have emerged demonstrating that autophagy, working in tandem with ubiquitin, also contributes to a selective-degradation process [3]. Accordingly, it is plausible that both proteasomal degradation and autophagy are interrelated, using ubiquitin as a common marker of proteins destined for degradation. Proteolysis is indispensable to a wide variety of cellular events because it can impact biological pathways irreversibly and in a spatiotemporal fashion. Proteolysis is also integral to the elaborate quality-control mechanisms that ensure steady-state levels of proteins (proteostasis), and it is becoming clear that the failure of this control leads to a variety of neurodegenerative disorders[4,5]. Indeed, protein misfolding, aggregation, and deposition are common components of many neurodegenerative disorders including Alzheimer's disease (AD) and Parkinson's disease (PD). The accumulation of damaged or abnormally modified proteins may lead to perturbed cellular functions and eventually to neuronal death, ultimately manifesting as neurodegenerative disease.

This highlights the importance of the cellular surveillance system, including the degradative pathways of the proteasome and autophagy. Another important aspect of the cellular surveillance system is the molecular chaperones that refold misfolded proteins, helping to prevent cellular toxicity. However, chaperone function is beyond the scope of this review. Here, we will focus on the consequences of neuronal proteasome and autophagy deficiency leading to neurodegenerative disorder(s), and will discuss several remaining issues that await further clarification.

2. Ubiquitin and neurodegeneration

Ubiquitin tags proteins that are destined for degradation by a post-translational modification in which the ubiquitin is attached through an isopeptide linkage between its terminal carboxyl-residue and a particular lysine-residue on the target protein. Since its discovery around 1980, the biochemical and molecular mechanisms of ubiquitinylation have been clarified through extensive studies [6]. Today, it is established that this posttranslational modification is catalyzed through the coordinated actions of the three types of enzymes: ubiquitin-activating

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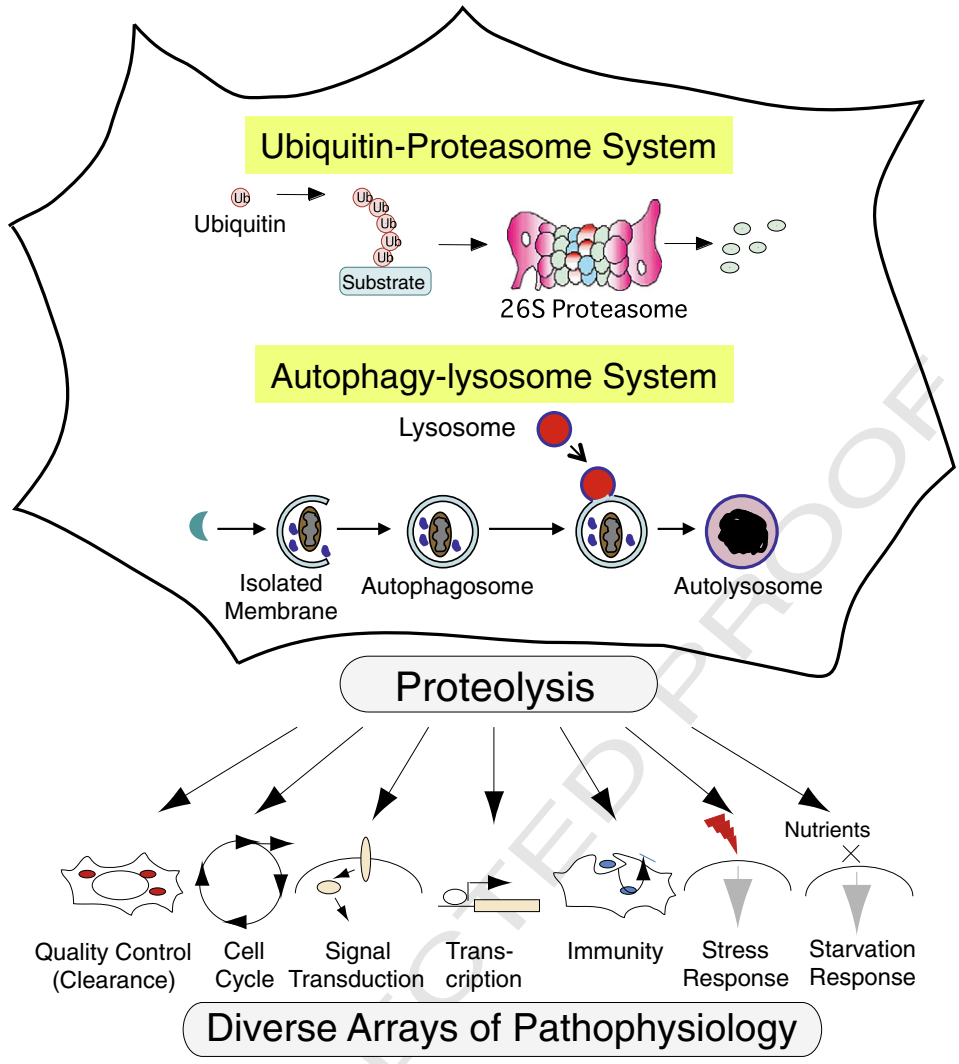

Fig. 1. Intracellular proteolysis is broadly classified into two distinct pathways consisting of the ubiquitin–proteasome and autophagy–lysosome, which are linked to a variety of physiological and pathological mechanisms in eukaryotic cells.

(E1), -conjugating (E2), and -ligating (E3) enzymes. Spectacularly, ubiquitin can itself be the target of another ubiquitin molecule, with multiple rounds of repeated ubiquitinylation leading to the formation of a so-called polyubiquitin chain. Ubiquitin possesses seven lysine residues, including those at positions 48 and 63, and an N-terminal methionine residue, all of which can nucleate polymer chains [7,8]. While the biological roles of polyubiquitin remain largely obscure, it has been shown that the K48-linked ubiquitin-polymer chain is the primary degradation signal for the proteasome, while the K63- and Met-linked linear polyubiquitin chains do not typically function as proteasomal-degradation signals. Instead, the latter participate in other processes, *e.g.*, transcriptional regulation, signal transduction, DNA repair, and membrane trafficking. Moreover, K63-linked polyubiquitinylation may also serve as a marker for autophagy, although this proposal remains under debate.

Ubiquitin is encoded by two distinct types of genes consisting of mono- and poly-ubiquitin genes. The numbers of poly-ubiquitin genes and their degree of tandem ubiquitin polymer differ by species. Surprisingly, in what appears to be a universal feature of eukaryotic species examined to date, at least two monoubiquitin genes are fused with ribosomal protein genes. The precise biological significance of this fusion of two proteins with apparently opposite functions remains unknown. In yeast, the polyubiquitin gene is indispensable under thermal stress, but not under normal growth conditions [9]. In other words, the free ubiquitin levels are adequate under normal conditions, but supplies must be rapidly increased for substrate conjugation under stress conditions. As excess ubiquitin levels are harmful, ubiquitin homeostasis is tightly controlled. In yeast, it has been shown that a balance is maintained between a deubiquitinylating enzyme and its inhibitor [10]. In mice, ubiquitin is encoded by two constitutively expressed monoubiquitin (Uba) genes and two polyubiquitin genes, Ubb and Ubc, that are stress inducible. Whereas targeted disruption of Ubb results in male and female infertility due to the failure of meiotic progression [11], Ubc-deficient mice die *in utero* between embryonic days 12.5 and 14.5, stressing the importance of homeostatic cellular ubiquitin levels [12].

In the late 1980s, ubiquitin was found to be a component of paired helical filaments (tau proteins) in Alzheimer's disease (AD) [13]. It remains true that an abnormal enrichment of ubiquitin in an inclusion body is a hallmark of various neurodegenerative disorders. The major molecules associated with various diseases include α-synuclein with Parkinson's disease (PD) and Lewy body dementia, polyglutamine tracts with Huntington's disease, and TDP-43 (TAR-DNA binding protein of 43 kDa) with frontotemporal lobar degeneration (FTLD) and amyotrophic lateral sclerosis (ALS) [14]. To date, the significance of finding ubiquitin and/or ubiquitin polymer(s) in inclusion bodies remains to be determined. Nonetheless, there are numerous clinical reports demonstrating that ubiquitin is a diagnostic feature of most

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