Neurobiology of Learning and Memory 138 (2017) 98–110

Contents lists available at ScienceDirect

Neurobiology of Learning and Memory

journal homepage: www.elsevier.com/locate/ynlme

Proteolysis, synaptic plasticity and memory

Ashok N. Hegde

Department of Biological and Environmental Sciences, Georgia College and State University, Milledgeville, GA 31061, USA

ARTICLE INFO

Article history:
Received 16 May 2016
Revised 25 August 2016
Accepted 5 September 2016
Available online 7 September 2016

Keywords:
Ubiquitin
Proteasome
Local protein degradation
Long-term potentiation
Long-term depression
Memory

ABSTRACT

Protein degradation has many critical functions in the nervous system such as refinement of synaptic connections during development and synaptic plasticity and memory in the adult organisms. A major cellular machinery of proteolysis is the ubiquitin-proteasome pathway (UPP). The UPP precisely regulates proteolysis by covalently attaching ubiquitin, a small protein, to substrates through sequential enzymatic reactions and the proteins marked with the ubiquitin tag are degraded by complex containing many subunits called the proteasome. Research over the years has shown a role for the UPP in regulating presynaptic and postsynaptic proteins critical for neurotransmission and synaptic plasticity. Studies have also revealed a role for the UPP in various forms of memory. Mechanistic investigations suggest that the function of the UPP in neurons is not homogenous and is subject to local regulation in different neuronal subcompartments. In both invertebrate and vertebrate model systems, local roles have been found for enzymes that attach ubiquitin to substrate proteins as well as for enzymes that remove ubiquitin from substrates. The proteasome also has disparate functions in different parts of the neuron. In addition to the UPP, proteolysis by the lysosome and autophagy play a role in synaptic plasticity and memory. This review details the functions of proteolysis in synaptic plasticity and summarizes the findings on the connection between proteolysis and memory mainly focusing on the UPP including its local roles.

1. Introduction

The quest for understanding how the nervous system stores information has led to the exploration of synaptic plasticity and memory in several model systems: from worms to human beings. Many decades of research in the 20th century focused on the role of protein synthesis in long-term synaptic plasticity and memory. Research that began in the 1990s revealed a role for regulated proteolysis in long-term synaptic plasticity. Protein degradation that functions to sculpt synapses and thus in aiding memory formation occurs mainly through the ubiquitin-proteasome pathway. Evidence over the last few years has also indicated a role for other types of proteolysis that occur through the lysosome and autophagy. This review mainly focuses on ubiquitin-proteasome-mediated degradation and provides brief descriptions of the functions of the lysosome and autophagy.

2. The ubiquitin-proteasome pathway

In the ubiquitin-proteasome pathway (UPP), covalent attachment of ubiquitin, a highly conserved 76-amino acid protein, to substrate proteins marks them for degradation by a proteolytic complex called the proteasome. The attachment of ubiquitin (ubiquitination) to proteins requires sequential activity of three enzymes (E1, E2, and E3) (Fig. 1). There are two E1s in many organisms but multiple genes encoding E2s exist.

In the UPP, an E1 activates ubiquitin and passes it onto an E2 which can transfer ubiquitin to the substrates directly or through generation of E3∼ubiquitin thioester intermediates. The substrate-specificity of ubiquitin ligation is largely determined by E3s. The first ubiquitin is covalently attached to the ε amino group of lysine residues in the substrate. After these enzymes attach the first ubiquitin to the substrate protein, to an internal lysine residue a second ubiquitin is attached and thus several ubiquitin molecules are attached to the growing chain which is termed "polyubiquitin". Substrates that are destined for degradation by the proteasome carry a specific polyubiquitin linkage. Every successive ubiquitin is attached to the 48th lysine residue in the previous ubiquitin (Glickman & Ciechanover, 2002; Hegde, 2010a). It must be noted, however, that ubiquitin attachment to other ubiquitin molecules could occur through any of the seven lysine residues in ubiquitin. For marking the substrate for ubiquitin-proteasome-mediated degradation, additional ubiquitin are attached to the first ubiquitin at its 11th or 48th Lys residue. Lys-63 linked polyubiquitin chains modulate protein function such as NFκ-B activation (Deng et al., 2000). There are instances when polyubiquitin chains are formed through second ubiquitin linkage to Lys-6, Lys-27, Lys-29 and

E-mail address: ashok.hegde@gcsu.edu

http://dx.doi.org/10.1016/j.nlm.2016.09.003
1074-7427/

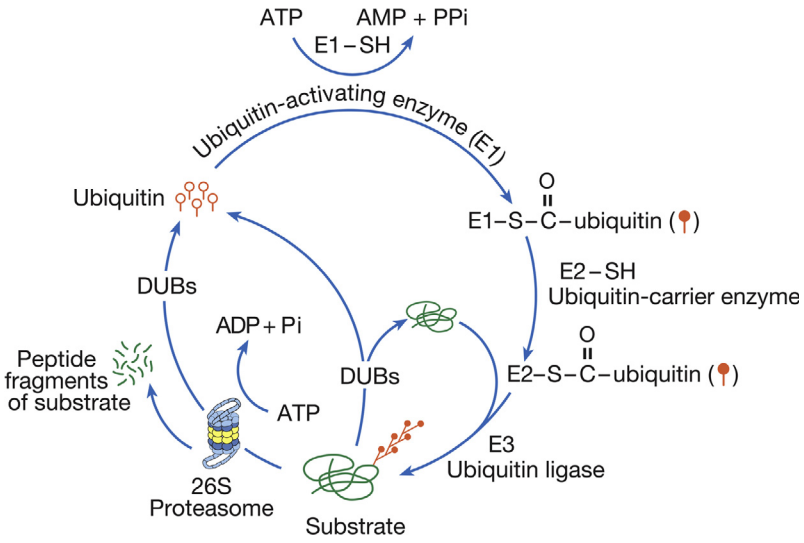

Fig. 1. The ubiquitin-proteasome pathway. In this proteolytic pathway, ubiquitin (single ubiquitin molecule is represented by open circles with straight tails) is selectively and covalently attached to the substrate. The enzymatic process of attaching ubiquitin to substrates depends on the action of three different classes of enzymes E1, E2 and E3. First, ubiquitin is activated by E1 to form a ubiquitin-AMP intermediate. Activated ubiquitin (closed circles with straight tails) is passed on to E2 (ubiquitin carrier enzymes). E2s transfers ubiquitin to an E3 (ubiquitin ligase) which ligates the activated ubiquitin to the substrate. To the ubiquitin attached to substrate another ubiquitin is attached and thus through successive linkages of ubiquitin a polyubiquitin chain forms. Polyubiquitinated substrates are degraded by a multi-subunit proteolytic complex called the 26S proteasome in an ATP-dependent reaction. Ubiquitin is not degraded but the polyubiquitin chain is disassembled and ubiquitin is recycled by deubiquitinating enzymes (DUBs). Before being committed to be degraded by the proteasome, ubiquitination is reversible. DUBs can disassemble the polyubiquitin chain if a substrate is ubiquitinated erroneously and prevent the degradation of the substrate. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Lys-33 of the first ubiquitin attached to the substrate are known to occur (Komander, 2009; Ye & Rape, 2009). Polyubiquitin chains contain mixed type of linkage between ubiquitin molecules such as through Lys-11 and Lys-48 in the same chain. Furthermore, ubiquitin itself can be posttranslationally modified through acetylation and phosphorylation (Ohtake et al., 2015; Swaney, Rodriguez-Mias, & Villen, 2015).

The E3 enzymes that ligate ubiquitin to substrate proteins are the most diverse in the UPP. There are two major classes of E3s: (1) HECT (homologous to E6-AP carboxyl-terminus) domain E3s, (2) RING (really interesting new gene) finger E3s. The RING finger E3s in turn can be divided into two classes SCF (SKP1-cullin-F-Box protein) and APC (Anaphase promoting complex). The specificity of the ubiquitin conjugation reaction, although largely occurs at the E3 ligation step, specific interactions between E2s and E3s and the type of ubiquitin linkage (Lys-48, Lys-63 and so on as described above) all add to the "combinatorial coding" of specificity in the ubiquitin conjugation reaction (Hegde, 2010b).

The protein substrate marked by polyubiquitin attachment is then degraded by the proteasome to small peptides and amino acids (Fig. 1). The polyubiquitin chains are not degraded but disassembled by deubiquitinating enzymes (DUBs) and the free ubiquitin molecules are recycled (Fig. 1). There are two types of DUBs. The category called ubiquitin C-terminal hydrolases (UCHs) is characterized by low molecular weight. The second class is that of high molecular weight DUBs which are called ubiquitin-specific proteases (UBPs or USPs). Apart of structural differences, UCHs and UBPs functionally differ with respect to substrates on which they act (Wilkinson, 2000).

The proteasome that functions to degrade the substrate proteins marked by polyubiquitin chain attachment is called the 26S proteasome based on its sedimentation coefficient during ultracentrifugation. It comprises a cylindrical catalytic 20S core and two regulatory complexes (RC) that are attached to either end of the 20S. The 20S consists of two outer rings with seven α subunits (α1 to α7) in each ring and two inner rings consisting of seven β subunits (β1 to β7). The catalytic activity of the proteasome is conferred by three of the seven β subunits (β1, β2 & β5). The catalytic sites in these β subunits are located at their N-termini which are inside the catalytic cavity which has a narrow opening of 13 Å in diameter (Cheng, 2009). Because of this, only an unfolded substrate can enter the catalytic core. It is thought that the unfolding activity is provided by the ATPases that are present in the base of the 19S RC which contains six ATPase subunits Rpt1-Rpt6 (Regulatory particle ATPase 1–6) and four non-ATPase subunits Rpn1, Rpn2, Rpn10 & Rpn13 (Regulatory particle non-ATPases 1, 2, 10 & 13). The 19S RC also consists of the 'lid' which includes only non-ATPase subunits (Rpn3, Rpn5, Rpn6-9, Rpn11, Rpn12, & Rpn15) (Hegde, 2010a; Marques, Palanimurugan, Matias, Ramos, & Dohmen, 2009).

Among the Rpn subunits, Rpn11 (also called Poh1) and Rpn13 (also called Uch37) are DUBs that are integral part of the 19S RC that assist in deubiquitination of the substrate as it is unfolded and threaded into the catalytic chamber of the 20S core. Another DUB called Usp14 (also known as Ubp6) reversibly associates with the Rpn1 and stimulates substrate degradation through deubiquitination (Leggett et al., 2002; Peth, Besche, & Goldberg, 2009). Two Rpn subunits, Rpn10 (S5) and Rpn13, have a role in recognizing the polyubiquitin chain (Baboshina & Haas, 1996; Husnjak et al., 2008; van Nocker, Deveraux, Rechsteiner, & Vierstra, 1996).

In neurons, the proteasome has widespread roles as will be explained later. Although there have not been extensive studies of individual subunits of the proteasome, at least one ATPase subunit, Rpt6, is known to have a role in activity-dependent growth of dendritic spines and the function of Rpt6 is regulated by NMDA receptor (NMDAR)- and CaMKII- mediated phosphorylation (Hamilton et al., 2012).

3. The UPP and long-term synaptic plasticity

Ubiquitin was familiar to researchers as a marker for brain pathology such as neurofibrillary tangles in Alzheimer's disease