CHAPTER 10

From Creator to Terminator:
Co-Chaperones That Link Molecular Chaperones
to the Ubiquitin/Proteasome System

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Abstract

Molecular chaperones are well known as intracellular mediators of protein folding. An active participation in protein degradation only recently emerged from the functional characterization of certain co-chaperones. In the light of these novel findings long held views regarding the interplay of chaperones and proteases in protein quality control need to be reconsidered. A further elucidation of chaperone-assisted degradation will be essential to understand the molecular basis of protein homeostasis.

Abbreviations


Introduction

It is textbook knowledge that molecular chaperones mediate intracellular protein folding. Their ability to bind and stabilize nonnative conformations of newly synthesized or damaged proteins enables molecular chaperones to facilitate the adoption of the native, biologically active structure.1-3 The same ability, however, makes molecular chaperones ideally suited to assist protein degradation. By maintaining misfolded or aggregation-prone proteins in a soluble state chaperones could ensure recognition by cellular degradation machineries, such as the ubiquitin/proteasome system, and promote proper disposal. In recent years more and more data have emerged that support a degradation function of at least some molecular chaperones, e.g., members of the Hsp70 and Hsp90 chaperone families.4-6 Their cooperation with the

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ubiquitin/proteasome system is mediated by a set of dedicated co-chaperones. In the following we will describe these co-chaperones, the functional characterization of which has significantly expanded our understanding of intracellular protein quality control. At the same time novel questions arise. What regulates the balance between chaperone-assisted protein folding and degradation? Is the chaperone system able to discriminate between nonnative proteins doomed for degradation and those that need to be refolded? Answers to these questions have only begun to emerge. Addressing them may pave the way to therapeutic modulation of chaperone pathways in neurodegenerative diseases and cancer in the future.

The Ubiquitin/Proteasome System

Before we will describe how chaperone activity can be switched from protein folding to protein degradation—how the creator is turned into a terminator—it appears necessary to introduce the ubiquitin/proteasome system, which is the main degradation machinery for the removal of misfolded and short lived proteins in the eukaryotic cytoplasm and nucleus and which mediates ER-associated degradation.\(^7\)_8 As the name says the system comprises two main components: (i) ubiquitin—a small protein of 76 amino acids that is expressed in all eukaryotic cells and serves as a degradation signal when conjugated onto other proteins in the form of a polyubiquitin chain,\(^9\) and (ii) the proteasome—a large oligomeric protein complex with a central proteolytic cavity in which polyubiquitylated proteins can be degraded in a manner separated from the cellular surrounding.\(^10\) This brief description already points to distinct steps during the degradation process. The protein doomed for destruction has to be modified by ubiquitin chain attachment, which requires the activation of ubiquitin and the specific recognition of the protein substrate by a conjugation machinery, followed by sorting to the proteasome and proteolytic cleavage inside the proteasome cavity. Ubiquitin activation is mediated by a single ubiquitin-activating enzyme, termed E1, and involves the formation of a thioester bond between the C-terminal glycine of ubiquitin and a cysteine residue of the enzyme (Fig. 1). The activated ubiquitin is transferred onto the E2 ubiquitin-conjugating enzyme involving again thioester bond formation, before covalent attachment to lysine residues of the protein substrate is assisted by an E3 ubiquitin ligase.\(^9\)_11 Lysine residues of the attached ubiquitin itself are subsequently used for the conjugation of additional ubiquitin moieties, leading to chain formation (Fig. 1). A lysine-48 linked chain usually serves as the degradation signal. In some instances, chain formation requires additional proteins that cooperate with the E2/E3 machinery.\(^12\) Thirty-four distinct E2s for ubiquitin conjugation are present in the human genome, all