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Review

Protein degradation and the stress response

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ABSTRACT

Environmental stresses are manifold and so are the responses they elicit. This is particularly true for higher eukaryotes where various tissues and cell types are differentially affected by the insult. Type and scope of the stress response can therefore differ greatly among cell types. Given the importance of the ubiquitin proteasome system (UPS) for most cellular processes, it comes as no surprise that the UPR plays a pivotal role in counteracting the effects of stressors. Here we outline contributions of the UPS to stress sensing, signaling, and response pathways. We make no claim to comprehensiveness but choose selected examples to illustrate concepts and mechanisms by which protein modification with ubiquitin and proteasomal degradation of key regulators ensures cellular integrity during stress situations.

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1. Introduction

Cells constantly have to battle diverse situations that endanger cellular and genomic integrity. Products of metabolic processes cause some of these stresses internally; a changing environment causes others. Regardless of the cause, cells need to have processes in place to sense the stress, transduce the information, and induce proper counter measures, including adaptation to the new environment to guarantee the survival of the cell or organism (Fig. 1). Cellular integrity may be preserved by repair of the stress-induced damage or by degradation and replacement of heavily damaged macromolecules. When these counter measures are insufficient, cells choose more radical actions such as apoptosis or macroautophagy to protect the organism. The major targets of insults are macromolecules like DNA, mRNAs, proteins, and lipids. Damage to these structural components and important regulators can compromise cellular and genomic integrity. Stress response pathways therefore often evoke cell cycle arrest to avoid distribution of damaged macromolecules, particularly damaged DNA, to daughter cells.

Proteolysis by the proteasome plays an important role in stress response pathways. One important function is the removal of damaged proteins to avoid accumulation as potentially harmful aggregates and to eliminate proteins with compromised activity. In many cases this degradation pathway is not protein specific but recognizes features characteristic for damaged proteins

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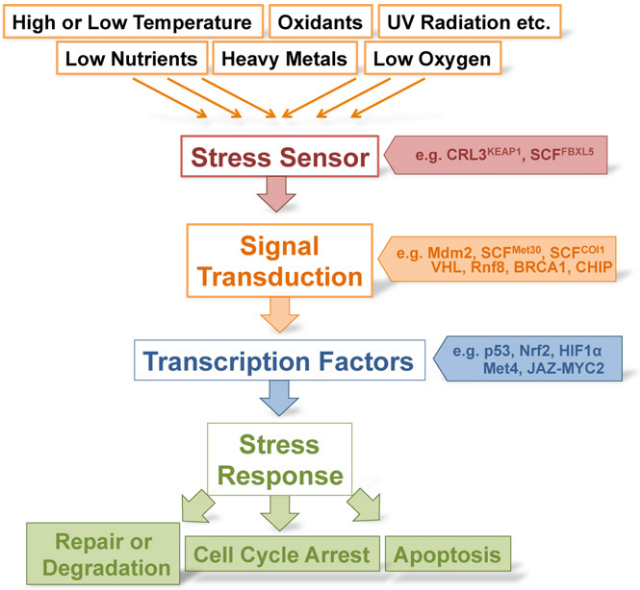

Fig. 1. The stress response. Stress response requires sensing of stress, and transduction of the signal to response elements that induce gene expression programs to counteract stressors. A few selected examples for ubiquitin ligases functioning at distinct steps of the stress response are indicated.

(for example oxidized or misfolded). In some cases this proteasome pathway may be partly independent of ubiquitylation (e.g. oxidative stress). In addition, selective ubiquitylation and degradation of regulatory factors coordinate stress response processes. A common theme here is that a normally unstable transcription factor is stabilized by stress signals, and then induces a transcriptional program to coordinate removal of damaged components, cell cycle arrest, and adaptation (e.g. p53, Nrf2, HIF1).

This review will give a short overview about the ubiquitylation process and discuss concepts of the ubiquitin proteasome system (UPS) in stress sensing, signaling and response pathway activation. A major stress response pathway with extensive involvement of the UPS is the reaction to various kinds of DNA damage. A review article in this issue is devoted to the DNA damage response [A. Peyroche, this issue]. Similarly, protein quality control pathways in different cellular compartments that play essential roles in survival of many if not most stress situations are discussed in a separate review article [R. Gardner, this issue]. We will therefore only very briefly examine these important stress response pathways here, and refer the interested reader to the accompanying reviews in this issue [R. Gardner and A. Peyroche, this issue] or other recent review articles [1,2]. However, we will briefly describe the role of the UPS in other common stress response pathways such as heat shock and hypoxia, as well as less known stress situations induced for example by aneuploidy. Finally we will briefly examine the important role of stress response and proteolysis for human health as they counteract stress as a potent inducer of cancer, aging, and neurological disorders.

2. Ubiquitylation

The small 76 amino acid protein ubiquitin is covalently attached to typically lysine residues, or the N-terminus in target proteins to form a posttranslational modification that regulates most cellular and developmental processes. Ubiquitylation can come in the form of mono, poly, or multiubiquitylation [3–7]. This complexity of the ubiquitin signal is further increased because there are 7 lysine residues (K6, K11, K27, K29, K33, K48 and K63) as well as the amino-terminus in ubiquitin that can be used to form distinct polyubiquitin chains [8–11]. The various chain topologies are structurally diverse and can define different functions of the ubiquitin chain, such as targeting proteins for proteasome-dependent proteolysis, or modulation of protein function, structure, assembly, and localization.

Ubiquitin is attached to substrates by the E1–E2–E3 cascade of enzymes, consisting of ubiquitin activating enzymes (E1s), ubiquitin conjugating enzymes (E2s), and finally the ubiquitin ligases (E3s) [7]. Ubiquitin activation is an energy dependent process, which initiates the cascade that culminates in formation of an isopeptide linkage, typically between a lysine residue of the substrate and the terminal carboxyl group of ubiquitin. This step is usually achieved via ubiquitin ligases, which are responsible for substrate recognition and stimulation of E2 activity. E3s are therefore central to the ubiquitylation process and govern most processes in cells. This is accentuated by the fact that there are more ubiquitin ligases encoded in the human genome (estimated 600–1000) than there are protein kinases (518) [12].

3. Concepts of cellular stress response

Cellular strategies to battle various stresses vary, but we can distinguish three general phases: stress sensing, signaling, and response (Fig. 1). Typically cells do not sense the stressors themselves but rather their consequences such as damaged macromolecules or the reduction in ATP production. It is however crucial that the stress situation is detected before major damage occurs so that cells have time to activate response and adaptation mechanisms. Once the stress has been detected, cells transduce the signal to ensure that the appropriate countermeasures are induced. This usually involves cascades of posttranslational protein modifications, especially phosphorylation. The stress signal ultimately reaches transcription factors to activate a stress response program by modulation of gene expression profiles. The subsequent increase in repair and defense capacities may be sufficient for adaptation to the stress condition, but depending on the severity of the damage, cells may trigger more drastic measures like apoptosis or senescence to protect the tissue or organism. Most stressors induce not just a single response pathway, but a network of usually integrated pathways to deal with multiple different types of damages. This is an important feature of effective stress response because a single stress situation can lead to different damages. For example oxidative stress not only leads to oxidized proteins and lipids that need to be removed, but also induces DNA damage.

The ubiquitin proteasome pathway plays important roles at all levels of stress response. The increased need for protein modification by ubiquitin is evident from dedicated stress-inducible ubiquitin genes in all eukaryotes. Among the 4 ubiquitin genes in yeast (*UBI1-4*), *UBI1-3* generate ubiquitin during normal growth, and the polyubiquitin gene *UBI4* (five head-to-tail repeats) compensates for the increased need during stress [13,14]. Mammals also have 4 ubiquitin genes (*UbA52*, *UbA80*, *UbB*, *UbC*), and the two polyubiquitin genes *UbB* and *UbC* are stress induced [15]. Even though ubiquitin is mostly recycled before ubiquitylated substrates enter the proteasome, basal turnover of ubiquitin results in approximate half-lives of 2 and 30 h in yeast and mammals, respectively [16,17]. Increased protein ubiquitylation during stress accelerates ubiquitin turnover. Interestingly, low levels of free ubiquitin present a cellular stress situation known as *ubiquitin stress* that is counteracted by increased transcription and enhanced disassembly of ubiquitin conjugates [18,19]. In addition, ubiquitin stress in yeast triggers a change in proteasome composition through increased association of the deubiquitylating enzyme Ubp6 and subsequent enhanced ubiquitin recycling [20]. The human Ubp6 ortholog Usp14 may have similar functions in mammals. Limiting the availability of ubiquitin by deletion of stress induced