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Graphical Review

# The proteasome and the degradation of oxidized proteins: Part III—Redox regulation of the proteasomal system

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ABSTRACT

Here, we review shortly the current knowledge on the regulation of the proteasomal system during and after oxidative stress. After addressing the components of the proteasomal system and the degradation of oxidatively damaged proteins in part I and II of this series, we address here which changes in activity undergo the proteasome and the ubiquitin-proteasomal system itself under oxidative conditions. While several components of the proteasomal system undergo direct oxidative modification, a number of redox-regulated events are modulating the proteasomal activity in a way it can address the major tasks in an oxidative stress situation: the removal of oxidized proteins and the adaptation of the cellular metabolism to the stress situation.


**Contents**



## Introduction

The main task of the ubiquitin-proteasomal-system (UPS) is the maintenance of a functional proteome of the cell. The UPS consist of two major pathways, the ATP-dependent 26S proteasome, degrading polyubiquitinated substrates formed by the polyubiquitinating enzymatic machinery and the ATP-independent 20S proteasome-catalyzed degradation pathway [1,2]. While interestingly, the 26S proteasomal pathway is responsible for the degradation of a vast majority of regulator proteins, the 20S proteasome is responsible for the degradation of oxidized proteins [3]. Therefore, during oxidative stress the proteasomal system has to be adapted to the stress situation ensuring a cellular regulatory response and the degradation of oxidized proteins, as oxidative stress is not only involving cellular damage, but also redox-regulation [4,5]. This damage and regulation is reflected also in proteasomal modifications (Fig. 1). One of the more prominent modifications is the glutathionylation of the proteasome. During oxidative stress, the cellular redox-state shifts and the ratio of cellular reduced and oxidized glutathione shifts leading to a modification of several proteasomal subunits. In addition to that several direct oxidative modifications of the proteasome are taking place, including protein oxidation leading to proteasome carbonylation, proteasomal glycoxidation and modification with lipid peroxidation products (Fig. 1). It is assumed, that these modifications modulate the proteasomal activity. However, to which extent these modifications impair the proteasomal activity remains unknown today. Several reports demonstrated that only high levels of damage to the 20S proteasome lead to a catalytic impairment [6,7], whereas the 26S proteasome is more susceptible towards oxidative damage [7,8].

Due to the requirement of an enhanced turnover of regulatory proteins in a stress situation and the necessity to degrade oxidized proteins, several components of the UPS are under the control of stress-related transcription factors. One of those is the Nrf2-Keap1-system [9]. So, oxidative stress is also able to induce *de novo* synthesis of proteasomal subunits and parts of the UPS (Fig. 2). Interestingly, the parts of the UPS are not only target genes of Nrf2, but the UPS itself is also involved in the degradation of Keap1. The Keap1-Cul3-Rbx-complex is catalyzing the polyubiqutination of Nrf2, making it a substrate for the 26S proteasome. During oxidative stress, Keap1 becomes oxidized and is unable to catalyze the polyubiquitination of

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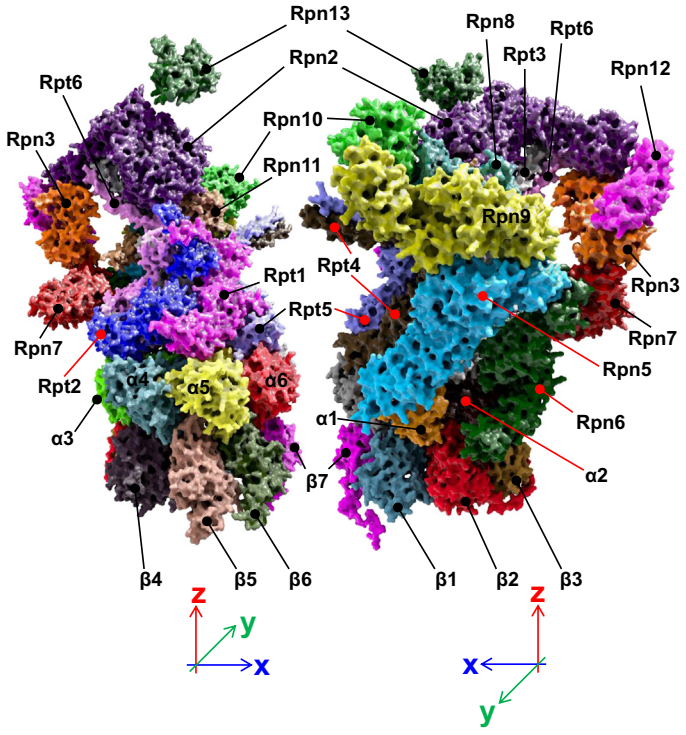


**Oxidation deriven sub unit modifications of the 20S proteasome and the19S regulator:**

| Subunit | HNE | PC | S-Glut. | Glyc. |
|---|---|---|---|---|
| α1 | X | | | X |
| α2 | X | X | | X |
| α3 | X | | | X |
| α4 | X | X | | |
| α5 | X | | X | |
| α6 | X | X | X | |
| α7 | X | | X | |
| β1 | X | | | |
| β1i | X | | | |
| β2 | | | | X |
| β3 | X | | | |
| β4 | X | | | X |
| β5 | X | | | X |
| β6 | X | | | X |
| β7 | X | | | |
| Rpn1 | | | X | |
| Rpn2 | | | X | |
| Rpn8 | | | | |
| Rpn11 | | | | X |
| Rpt1 | | | | X |
| Rpt2 | | | | X |
| Rpt3 | | X | | |
| Rpt4 | X | X | | |
| Rpt5 | | | | |
| Rpt6 | | | | |

**Fig. 1.** Oxidative modifications of the proteasomal system.

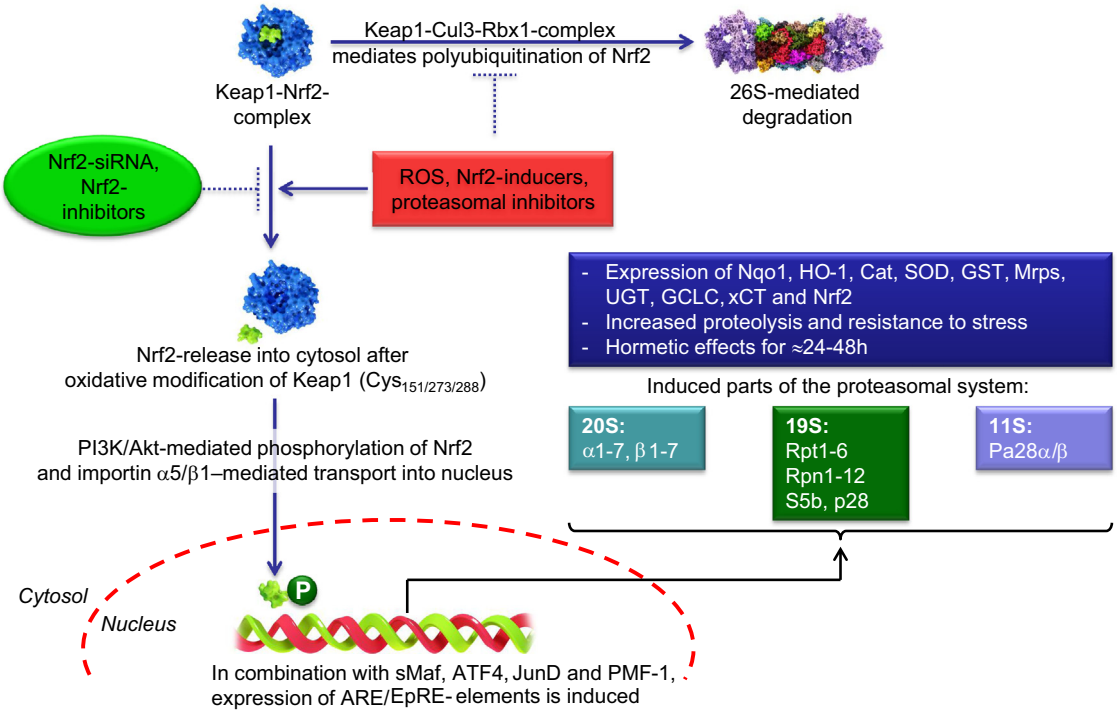


**Fig. 2.** *De novo* synthesis of the proteasomal system via Nrf2-mediated stress-response.

Nrf2. This is an example for the redox sensitivity of the ubiquitination system, which was described earlier [10,11]. Although a wide array of proteasomal subunits is regulated via Nrf2, for several proteasomal components other transcription factors are involved. Especially the inducible proteasomal subunits and the 11S proteasomal activator (also Pa28) [1,2] are under the control of the Jak/Stat pathway (Fig. 3). It was thought traditionally, that this pathway is only induced by the cytokine interferon-γ (IFN-γ), but more recently also stress related