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Control of SUMO and Ubiquitin by ROS: Signaling and disease implications

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ABSTRACT

Reversible post-translational modifications (PTMs) ensure rapid signal transmission from sensors to effectors. Reversible modification of proteins by the small proteins Ubiquitin and SUMO are involved in virtually all cellular processes and can modify thousands of proteins. Ubiquitination or SUMOylation is the reversible attachment of these modifiers to lysine residues of a target via isopeptide bond formation. These modifications require ATP and an enzymatic cascade composed of three classes of proteins: E1 activating enzymes, E2 conjugating enzymes and E3 ligases. The reversibility of the modification is ensured by specific isopeptidases. E1 and E2 enzymes, some E3 ligases and most isopeptidases have catalytic cysteine residues, which make them potentially susceptible for oxidation. Indeed, an increasing number of examples reveal regulation of ubiquitination and SUMOylation by reactive oxygen species, both in the context of redox signaling and in severe oxidative stress. Importantly, ubiquitination and SUMOylation play essential roles in the regulation of ROS homeostasis, participating in the control of ROS production and clearance. In this review, we will discuss the interplay between ROS homeostasis, Ubiquitin and SUMO pathways and the implications for the oxidative stress response and cell signaling.

1. Introduction

A major challenge in biology is to understand how cells sense their environment, integrate multiple information, transmit it, and make the appropriate decision. Signal transduction is the process by which a signal is transmitted from the sensor to the effector. This is ensured by several mechanisms, including for example allosteric regulation of enzymes by Ca^{2+} or post-translational modifications (PTM) of proteins (Deribe et al., 2010).

PTMs that are reversible modifications can act as molecular switches: They can rapidly activate or deactivate the molecular function of a target. Different categories of PTM are known. Proteins can be modified by a small chemical group, resulting in, for example, phosphorylation, acetylation or methylation of amino acid side chains. But post-translational modifications can also be as large as a small protein. The best-studied example of a post-translational modification by a small protein is the attachment of Ubiquitin (a 76 residues protein) to a target protein, a process called ubiquitination (Hershko and Ciechanover, 1998; Komander and Rape, 2012; Pickart, 2001; Pickart and Eddins, 2004; Swatek and Komander, 2016; Yau and Rape, 2016). Reversible modification of proteins by Ubiquitin is an ATP dependent process that involves enzymes able to add Ubiquitin to target proteins (writers), effector proteins recognizing this modification (readers), and enzymes removing the modification (erasers). After its discovery, several related proteins were identified that belong to the “Ubiquitin-like proteins” (Ubl) family, such as SUMO or NEDD8. Although similarity of Ubls with Ubiquitin can be low at the amino acid level, they all share a common tertiary structure known as the Ubiquitin fold (reviewed in Hochstrasser, 2000). Most Ubls are covalently attached to their targets by an enzymatic cascade analogous to that of Ubiquitin (Streich and Lima, 2014). Among the different Ubls, modification with the Small Ubiquitin-Like Modifier (SUMO), known as SUMOylation, has gained increasing interest because of its role in various signaling pathways and its broad range of targets (Flotho and Melchior, 2013; Gareau and Lima, 2010; Pichler et al., 2017).

More recently, oxidative modification of amino acids has emerged as an important mechanism of cell signaling, a concept known as redox signaling (Wall et al., 2012). Several amino acid side chains are susceptible to oxidation, including those of methionine, tyrosine and cysteine (Berlett and Stadtman, 1997). Of particular importance seems reversible oxidation of cysteines, which is currently an area of intense investigation. The thiol group of cysteine can adopt different oxidation states: first, from its deprotonated form (R-cys-S$^-$), its oxidation leads to the formation of sulfenic acid (R-cys-SOH). This species can in turn

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form a disulfide bond with another molecule or can get further oxidized to sulfinic acid (R-cys-SO_2H) and finally to sulfonic acid (R-cys-SO_3H). Whereas sulfinic and sulfonic acids are presumed to be irreversible, the sulfenic acid state can be reverted. Transient oxidation of cysteine residues can lead to transient alteration of the biological function of a protein and can trigger, amplify or shut down a signaling cascade. This mechanism has been well described for example for protein tyrosine phosphatases (Tonks, 2005). They possess a catalytic motif H-C-X_5-R (Tabernero et al., 2008), in which the catalytic cysteine is deprotonated. This is necessary for the dephosphorylation of their targets. In the presence of H_2O_2, this cysteine can be oxidized to sulfenic acid (Lee et al., 1998), which results in temporal inactivation of the phosphatase, favoring the amplification of the phosphorylation cascade upon growth factor signaling (Woo et al., 2010).

1.1. Undesired and deliberate ROS production

The main endogenous source of unwanted ROS generation in mammalian cells occurs during oxidative phosphorylation in mitochondria, where between 1 and 5% of the electrons could leak and produce superoxide radicals ($O_2^{\cdot-}$) that are rapidly converted to the less dangerous hydrogen peroxide (H_2O_2) by superoxide dismutases (Murphy, 2009). H_2O_2 can also be produced through action of xanthine oxidases, which is especially important in reperfusion damage (Granger and Kvietys, 2015), or in consequence of exposing cells to xenobiotics or chemotherapeutics (Pritsos, 2000).

ROS, and in particular H_2O_2, can also be produced in a deliberate way. The first phenomenon described was called “respiratory burst”, which takes place during phagocytosis in macrophages and neutrophils (Babior et al., 1973). This phenomenon generates a very corrosive mixture of ROS, participating in the destruction of the biological material in phagosomes. The enzyme responsible for the generation of ROS is a membrane-bound complex called NADPH oxidase 2 (NOX2). NOX2 uses NADPH and O_2 to produce $O_2^{\cdot-}$, which is in turn converted to H_2O_2 by superoxide dismutases (Lambeth, 2004). After this first example, numerous studies revealed that H_2O_2 can be produced by many cell types during cell signaling. For example, H_2O_2 is produced following treatment of cells with PDGF (Sundaresan et al., 1995), TGFβ1 (Ohba et al., 1994; Thannickal and Fanburg, 1995), IL1 (Meier et al., 1989), TNFα (Lo et al., 1996; Meier et al., 1989) and EGF (Bae et al., 1997). In each of these cases, $O_2^{\cdot-}$ is produced by enzymatic complexes that are related to the phagocytic NADPH oxidase. Seven NOX complexes (NOX1 to NOX5, DUOX1 and DUOX2), which are present in many different eukaryotic cell types, have been described so far (Lambeth, 2004). Their activities are tightly regulated and switched on by different stimuli such as growth factors.

Irrespective of whether ROS are an unwanted side product, endogenously produced by NADPH oxidase or caused by exogenous compounds, they can trigger two distinct but partially overlapping phenomena, redox signaling and oxidative stress.

1.2. Redox signaling

The term “Redox signaling” refers to molecular events in signal transduction that involve reversible oxidation of specific (non-random) amino acid side chains. Oxidation thus acts as a molecular switch in the signaling cascade. Famous examples are reversible inactivations of catalytic cysteines in tyrosine phosphatases (Tonks, 2005) or the lipid phosphatase PTEN. Redox signaling contributes to physiological processes, e.g. during EGF receptor signaling (Rhee, 2006; Woo et al., 2010) or in cell cycle progression (Sarsour et al., 2009). Redox signaling also contributes to many aspects of oxidative stress response, for example in *Saccharomyces cerevisae* when ROS induces formation of a specific disulfide-bond in the transcription factor Yap1, which inhibits its nuclear export and thereby induces Yap1-responsive antioxidant gene expression (Delaunay et al., 2000, 2002).

1.3. Oxidative stress

Oxidative stress can be defined as a situation in which endogenously produced or exogenously provided ROS exceeds the ROS scavenging capacity of the cells, and in which unwanted and random, often irreversible, oxidation of proteins, lipids and nucleic acids occurs (Schieber and Chandel, 2014; Sies et al., 2017). Whether oxidants will cause mild, severe or lethal oxidative stress is difficult to predict. It depends on the type and source of ROS, its concentration, exposure time and the buffering capacity of the cell. When ROS are endogenously produced, their effect may even be locally confined.

In this review, we focus on cysteine-dependent redox signaling, which in many studies is triggered by addition of hydrogen peroxide to cells. Evaluation of the literature is complicated by the fact that seemingly similar experiments may have highly divergent outcomes. The specific cell type strongly influences whether cells survive a specific treatment - and if not, whether they die within the first hours, days or weeks. Conversely, a wide range of ROS concentrations (1–1000 μM H_2O_2) is used to trigger specific responses in different cell lines (an example from our own work (Stankovic-Valentin et al., 2016),). A standard parameter that would allow to compare severity of treatments, for example clonogenic survival, would be highly desirable for the field.

Many enzymes involved in Ubl pathways are cysteine enzymes and are thus good candidates for redox regulation. Indeed, during the last years, several examples have emerged, in which Ubl enzymes are subject to redox regulation. The interplay between redox regulation and Ubiquitination or SUMOylation is the focus of this review. First, we will briefly introduce the mechanism and consequences of ubiquitination and SUMOylation. Then, we will focus on the biochemical details and biological consequences of the redox regulation of these pathways. Finally, we will briefly address how SUMO and Ubiquitin participate in ROS homeostasis.

2. Ubiquitin and SUMO pathways

2.1. The Ubiquitin pathway

2.1.1. Ubiquitin writers

Ubiquitination requires an enzymatic cascade composed of an E1 activating enzyme, an E2 conjugating enzyme and an E3 ligase (see Fig. 1). So far, only two Ubiquitin E1 enzymes have been identified, the Ubiquitin-specific E1 Uba1 and Uba6, which can activate Ubiquitin (Jin et al., 2007; Pelzer et al., 2007) and the Ubl FAT10 (Chiu et al., 2007). The Ubiquitin E1 enzyme contains several domains: an adenylation domain, an E2 binding domain called UFD (Ubiquitin Fold Domain) and the catalytic cysteine domain (Cys domain) (Schulman and Harper, 2009). The first step catalyzed by the E1 is the adenylation of Ubiquitin's C-terminal glycine, a reaction that required ATP. Once adenylated, Ubiquitin is transferred to the E1's catalytic cysteine, forming a thioester bond. How the catalytic cysteine of the E1 can reach this Ubiquitin-adenylate was an open question until the recent structural work on the related SUMO E1 enzyme (Olsen et al., 2010; Streich and Lima, 2014). The SUMO and Ubiquitin E1 enzymes share the same catalytic mechanism. Structural data from the SUMO E1 enzyme show that the Cys domain can rotate, which brings the catalytic cysteine of this domain in proximity to SUMO. This is accompanied by dramatic structural changes that additionally uncover the catalytic cysteine allowing the nucleophilic attack of the SUMO-adenylate, which results in an E1-SUMO thioester bond. The adenylation domain is then charged with a second SUMO, forming a ternary complex that consists of an E1 loaded with an adenylated and a thioester-linked SUMO. Next, the UFD domain of the E1 binds the E2 enzyme (Lee and Schindelin, 2008; Lois and Lima, 2005; Walden et al., 2003) and a subsequent rotation of this domain brings the catalytic cysteine of the E2 in close proximity to the thioester bound SUMO (Olsen and Lima, 2013), allowing the transfer of

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