Biochimica et Biophysica Acta 1843 (2014) 2878–2885

Contents lists available at ScienceDirect

Biochimica et Biophysica Acta

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

Review

Non-nuclear function of sumoylated proteins

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ARTICLE INFO

Article history:
Received 8 May 2014
Received in revised form 11 July 2014
Accepted 30 July 2014
Available online 7 August 2014

Keywords:
Autophagy
Cytoskeletal function
Enzyme activity
Exocytosis
Mitochondrial dynamics
Receptor function

ABSTRACT

Post-translational modification by the SUMO moiety is now regarded as one of the key regulatory modifications in eukaryotic cells. Up to now, plenty of sumoylated proteins have been found to be involved in nuclear processes such as chromatin organization, transcription and DNA repair as well as in other cellular functions. Since the number of data concerning sumoylated proteins and their function outside the nucleus has grown rapidly, in this review we summarized the results describing the non-nuclear role of SUMO substrates. In particular, we focused on the role of sumoylation in the regulation of channel activity, receptor function, G-protein signaling, activity of enzymes, cytoskeletal organization, exocytosis, autophagy and mitochondrial dynamics.

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1. Introduction

Sumoylation belongs to the same group of post-translational modifications as ubiquitination and neddylation [1] and involves the attachment of SUMO (small ubiquitin related modifier) molecule to the target protein through isopeptide bond formation. The SUMO protein, having a molecular mass of about 11 kDa, is highly conserved from yeast to humans [2]. There are four SUMO molecules, SUMO-1, SUMO-2, SUMO-3 and SUMO-4. SUMO-2 shares 95% identity in amino acid sequence with SUMO-3 and they are often referred to as SUMO-2/3. Presently, SUMO-2 and SUMO-3 cannot be distinguished by antibodies. SUMO-2/3 contains a flexible N-terminus, which seems to serve as an acceptor in SUMO chain formation [3]. The shared identity in amino acid sequence between SUMO-2/3 and SUMO-1 is ~45%. Interestingly, SUMO-1 shares ~18% identity with ubiquitin and has a similar three-dimensional structure that is characterized by a globular β-grasp fold [4]. Quantitative and qualitative analyses of SUMO-1 and SUMO-2/3 in vertebrate cells have shown that the amount of SUMO-2/3-modified targets is greater than the amount of SUMO-1 modified proteins [5]. Both SUMO-2/3 and SUMO-1 contain the C-terminal Gly-Gly motif which is exposed to proteolytic cleavage during the process of maturation. This motif is crucial in the isopeptide bond formation occurring between the SUMO and a lysine side chain of the target protein [6]. SUMO-4 is similar to SUMO-2/3 and its maturation might be inhibited by a unique proline residue located at position 90 [7]. Also, it is known that the SUMO-4 precursor can be cleaved by the stress-induced endogenous hydrolase which, in consequence, facilitates its attachment to target proteins [8].

Usually, SUMO is attached to a lysine residue located in the consensus sequence ψKxD/E, where ψ corresponds to a large hydrophobic amino acid, K is a lysine residue, x is any amino acid, E is a glutamic acid and D is an aspartic acid [9]. Presently some additional motifs responsible for SUMO attachment are known [10]. Interestingly, detailed analysis of many SUMO substrates has shown that E is preferred over D in the consensus motif [11]. It should be also mentioned that in many cases modification by SUMO might occur at lysine residues outside the consensus motif. The sumoylation process is catalyzed by three groups of enzymes: E1-activating enzyme, E2-conjugating enzyme and E3-ligases (Fig. 1). SUMO attachment proceeds as follows. E1 SUMO enzyme activates the SUMO C-terminus in an ATP-dependent manner and carries out the transfer of activated SUMO to E2 SUMO-conjugating enzyme. Next SUMO is transferred from E2 to the substrate with the assistance of one of several SUMO-protein ligases (E3s). The specificity of the reaction is related to the activity of E2 and E3 enzymes [12]. While there is a variety of E3-ligases, only one E1 activating enzyme (SAE1/2)

Abbreviations: CASK, calcium/calmodulin-dependent serine protein kinase; COS-7, African green monkey kidney fibroblast-like cell line; Drp1, dynamin-related protein 1; FAK, focal adhesion kinase; hnRNPA2B1, heterogeneous nuclear ribonucleoprotein A2B1; K2P, potassium selective, plasma membrane leak channels; KAP1, KRAB-ZFP-associated protein 1; KARs, kainate receptors; Kv, voltage-gated potassium channels; MAPK, mitogen activated protein kinase; mGluRs, metabotropic glutamate receptors; PIAS, protein inhibitor of activated STAT; PKC, protein kinase C; PTP1B, protein-tyrosine phosphatase 1B; Rac1, Ras-related C3 botulinum toxin substrate 1; RGS, regulator of G protein signaling; RGSZ1, regulator of G protein signaling Z1; RGSZ2, regulator of G protein signaling Z2; RhoGDI, Rho GDP dissociation inhibitor; RIM, Rab3-interacting molecule; SENPs, sentrin-specific proteases; TGF-β, transforming growth factor beta; TβRI, TGFβ type I receptor; TRPM4, transient receptor potential melastatin 4; SUMO, small ubiquitin related modifier; Ubc9, SUMO-conjugating enzyme; Vps, vacuolar protein-sorting 34

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http://dx.doi.org/10.1016/j.bbamcr.2014.07.018
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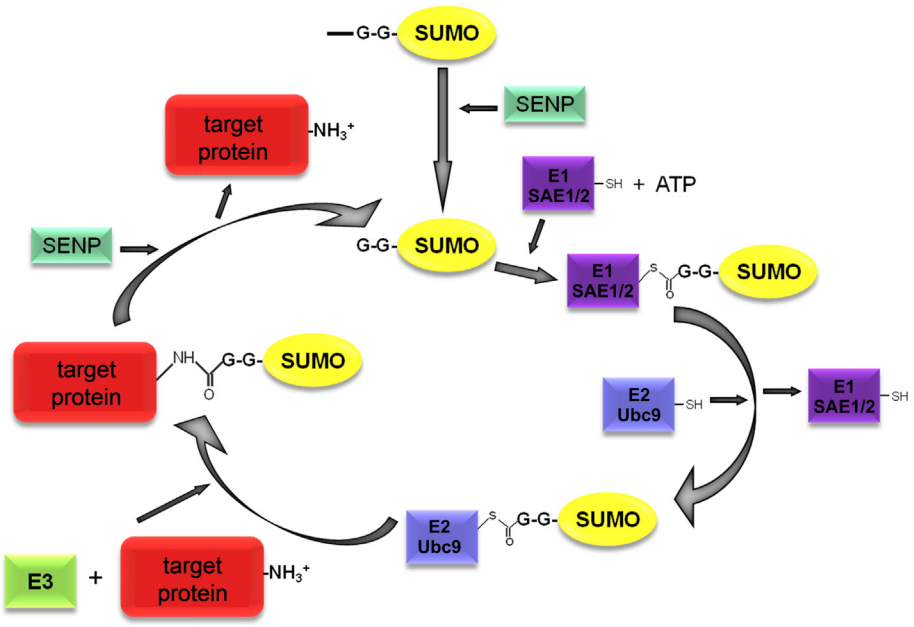

Fig. 1. A scheme illustrating the sumoylation process. E1, E2 and E3: enzymes involved in SUMO attachment to target proteins, SENP: SUMO-deconjugating enzyme.

and one E2-conjugating enzyme (Ubc9), are known. Even though Ubc9 catalyzes SUMO attachment, E3 ligases play an important regulatory role since they increase sumoylation efficiency and determine substrate specificity. SUMO E3 ligases with a RING-finger like domain belong to the family of SP-RING-containing proteins. This family is represented by PIAS (protein inhibitor of activated STAT) family proteins (PIAS1, PIAS3, PIASxα, PIASxβ and PIASy) in vertebrates and the Siz family proteins (Siz1 and Siz2) in *Saccharomyces cerevisiae* [13]. Another SUMO E3 ligase containing a domain distinct from the canonical RING type is RanBP2 [14]. Several other proteins have been also reported as E3 ligases. This group includes human polycomb 2 homologue (PC2) [15], histone deacetylase 4 (HDAC4) [16], topoisomerase I-binding RING finger protein (TOPORS) [17] and Ras homologue enriched in striatum (RHES) [18].

Sumoylation is a reversible modification. Detachment of SUMO is catalyzed by SUMO proteases, SENPs, also known as desumoylating enzymes. In mammalian tissues six such proteases have been described: SENP1–3 and SENP5–7. Among the SENP family, SENP1 and SENP2 show specificity toward SUMO-1 and SUMO-2/3 while SENP3 and SENP5–7 toward SUMO-2/3 [19,20]. Quite recently three other desumoylating enzymes have been found. These are DeSI1 (desumoylating isopeptidase 1), DeSI2 (desumoylating isopeptidase 2) and USPL1 (ubiquitin-specific protease-like 1) [21,22].

Sumoylation regulates many cellular functions, mainly by influencing protein–protein interactions [23]. SUMO attachment can mask protein–protein interaction sites, create a new binding interface or lead to conformational changes. The involvement of SUMO in the regulation of protein–protein interaction is often linked with the presence of a motif called SIM (Sumo Interacting Motif), that facilitates recognition of sumoylated proteins. The best characterized class of SIMs consists of a hydrophobic core ([V/I]-x-[V/I]-[V/I]) flanked by a cluster of negatively charged amino acids [24,25]. Interestingly, proteins undergoing sumoylation often bear SIM in their structure which allows them to form multiple protein complexes. To monitor protein–protein interaction/formation of complexes *in vivo*, the *trans*-SUMOylation assay has been elaborated [26]. Briefly, Ubc9 is fused with the protein of interest, protein 1. Upon interaction of protein 1 with the co-expressed protein 2, Ubc9 induces *trans*-SUMOylation of protein 2 which is manifested by a shift in its electrophoretic mobility. The *trans*-SUMOylation assay facilitates studies on protein–protein interactions at a level similar to that observed for endogenous proteins.

The very first protein described as a substrate of SUMO was RanGAP1 [27,28]. Up to now a lot of proteins that play a pivotal role in transcription, chromatin organization, DNA repair, telomere maintenance, nucleocytoplasmic transport, protein degradation or cell cycle regulation have been found to be modified by the SUMO molecule [2, 29–35]. It is well known that sumoylation might induce nuclear import of certain proteins [36]. There are some hints that nuclear export might be regulated in the same way [37,38]. Interestingly, apart from results concerning function of sumoylated proteins in the nucleus new exciting data about the role of SUMO substrates outside the nucleus have emerged recently [39]. At present it might be difficult to reconcile these findings with the common notion, substantiated by experimental data, that the enzymes responsible for sumoylation and desumoylation are enriched in the nucleus. However, there are results showing the presence of E1 and E2 in the cytoplasm of HeLa cells [36], E2 (Ubc9) in the endoplasmic reticulum [40] and SENP5 in the mitochondria [41]. Furthermore, it has been shown that the sumoylating enzymes operate at the cytoplasmic filaments of the nuclear pore complex [36] where they may contact/sumoylate cytoplasmic proteins. Thus, although how it occurs is not yet clear, the sumoylation of non-nuclear proteins is a fact well established.

The majority of data on non-nuclear SUMO targets concern the role of sumoylation in neuronal function [42–46]. It has been shown that sumoylation influences various aspects of neuronal activity including excitability or synaptic transmission [47–50]. The list of non-nuclear proteins whose function depends on sumoylation is very long [51], thus the present review is focused on the SUMO substrates for which the functional effect of sumoylation is quite well established (Table 1). In particular we describe, and illustrate in Fig. 2, the influence of protein sumoylation on channel activity, receptor function, G-protein signaling, enzyme activity, cytoskeletal organization, exocytosis, autophagy and mitochondrial dynamics.

2. Channel activity

Potassium selective, plasma membrane leak channels K2P, are known to control neuronal excitability [52]. One member of this family, K2P1, is sumoylated on lysine 274 which does not belong to a classical consensus motif. Interestingly, the SUMO-conjugating enzyme, Ubc9, has been found to associate with K2P1 in the plasma membrane. Also,

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