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Review

SUMO1/sentrin/SMT3 specific peptidase 2 modulates target molecules and its corresponding functions

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ABSTRACT

Small ubiquitin-like modifier (SUMOylation) is a reversible post-translational modification, which plays important roles in numerous biological processes. SUMO could be covalently attached to target proteins in an isopeptide bond manner that occurs via a lysine ε-amino group on the target proteins and the glycine on SUMO C-terminus. This covalent binding could affect the subcellular localization and stability of target proteins. SUMO modification can be reversed by members of the Sentrin/SUMO-specific proteases (SENPs) family, which are highly evolutionarily conserved from yeast to human. SENP2, a member of the SENPs family, mainly plays a physiological function in the nucleus. SENP2 can promote maturity of the SUMO and deSUMOylate for single-SUMO modified or poly-SUMO modified proteins. SENP2 can affect the related biological processes through its peptidase activity or the amino terminal transcriptional repression domain. It plays important roles by inhibiting or activating some molecular functions. Therefore, the research achievements of SENP2 are reviewed in order to understand its related functions and the underlying molecular mechanisms and provide a clue for future research on SENP2.

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1. Introduction

The Sentrin/SUMO-specific proteases (SENPs) family has six members, including SENP1, SENP2, SENP3, SENP5, SENP6 and SENP7 [1–3]. The hallmark of these proteases is that they have ~200 highly conserved amino acid sequences in the carboxyl-terminal domain, which is called the SENP domain [4]. Increasing evidences have been shown that SENP2 plays an important role in many biological processes.

SENP2 gene is located in human chromosome 3q27.2 or in the mouse chromosome 16B1. SENP2 protein localizes to the nuclear pore complexes (NPCs), the nucleoplasm, and the cytoplasm in subcellular localization [5,6]. SENP2 consists of 589 amino acids among which contains C-terminal catalytic structure of highly conserved amino acid residues 364–589 [7]. SENP2 has nuclear localization signal sequences (NLS) that are located at the N-terminal amino acids 28–52 and a leucine-enriched region at the amino acids 479–485 [6,8]. There are a high-affinity between the N-terminal of NLS in SENP2 and karyopherins (nuclear transport proteins), which could form a complex to promote the entry of SENP2 into the nuclear pore. Then SENP2 associates with the nucleoplasmic face of the nuclear pore complexes (NPCs) via interacting with the phenylalanine – glycine (FG) repeat region of nucleoporins (Nup153, Nup50, and Nup358/RanBP2) [9,10]. SENP2 has nuclear export signal (NES) sequences in amino acid residues 1–15, 143–155 and 317–332. These domains enable SENP2 to shuttle back and forth between the cytoplasm and nucleus, which are dependent on CRM1, a protein combining with the NES sequences in nuclear proteins to transport them out of the nucleus. SENP2 sub-cellular location may affect its capability to deSUMOylate substrates [5,11,12]. Besides, phosphorylation of the T368 site of SENP2 enhances SENP2 nuclear export function [13].

Just like other cysteine proteases, the active site of SENP2 is formed by a catalytic triad of amino acid residues that contains His478, Asp495 and Cys548 [7] (Fig. 1). The enzymatic characteristics of SENP2 have been confirmed in vivo and in vitro. SENP2 participates in the deSUMOylation of the target proteins through the activities of the isopeptidase and also involves in the maturation of SUMO precursors through endopeptidase activities. SENP2 has isopeptidase activities for catalyzing the de-conjugation between mature C-terminal glycine of SUMO and lysine of conjugated substrates [2]. SENP2 has endopeptidase activities for processing the pre-SUMO C-terminal sequence (-GG-ATY) into their mature form (-GG), the only known form of SUMO that can be activated and conjugated to other proteins [4]. For example, it has been shown that SENP2 can de-conjugate RanGAP-SUMO1/2/3 and hydrolyze these three SUMO precursors in vitro [14]. Although all SUMO subtypes can be identified and processed by SENP2, there are priorities: pre-SUMO-2>pre-SUMO-1>pre-SUMO-3 [7]. Similarly, the deSUMOylation of SENP2 has selectivity for poly -SUMO1/2/3 [15–17]. It has also been confirmed that SENP2 could deSUMOylate SUMO1/2/3 or enhance the maturation of three SUMO precursors in vivo [18,19].

It has been identified the role of SENP2 in inhibiting or activating some molecules' functions. Here, we reviewed the related papers to gain insight into the importance of the related functional regulation and the involved molecular mechanisms concerning SENP2.

2. SENP2 inhibits some molecules' functions via deSUMOylation

It has been reported that SENP2 could deSUMOylate NEMO, Drp1, ERK5, IRF3 and cGas-STING complex to negatively regulate NF-kB activation, the expression of P62, Rip53, adhesion molecules and the sustained activation of cGas, STING and IRF3 in DNA damage, mitochondria-dependent apoptosis, atherosclerotic plaques, and anti-DNA virus infection, respectively (Fig. 2).

2.1. NEMO

In response to DNA damage, SUMOylation of NF-kB essential modulator (NEMO) is important for NF-kB activation. NEMO is a member of IkB kinase (IKK) complexes that could regulate the activation of NF-kB to exert vital roles in cell death responses [20]. Lee et al. firstly reported that only SENP2 among the six known SENPs could effectively deSUMOylate NEMO to suppress NF-kB activation during DNA damage process. The negative feedback network between SENP2 and NF-kB could attenuate the DNA damage response to protect organism. Further researches found that NF-kB was recruited to NF-kB binding region of SENP2 promoter to induce the transcription of SENP2 when DNA damage was occurred. The activation transcription of SENP2 could enhance its expression and then promote the deSUMOylation of NEMO to limit

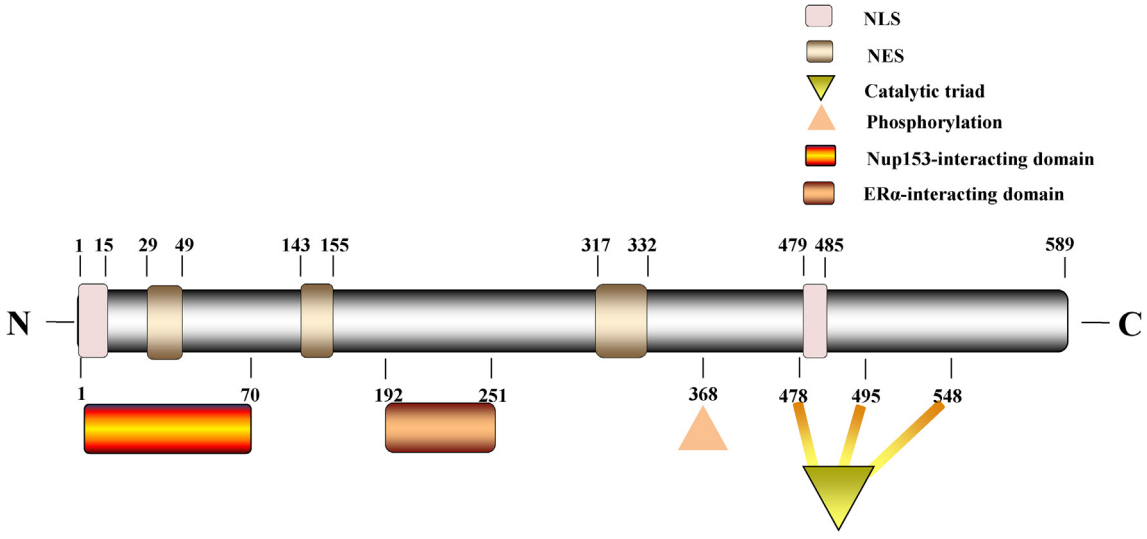

Fig. 1. The functional domain of SENP2 protein.