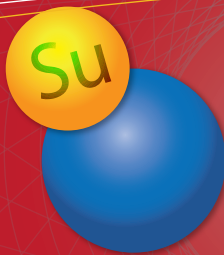




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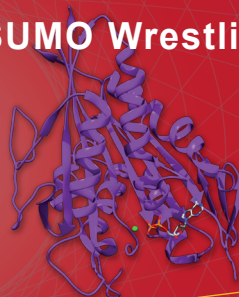
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SUMO Wrestling: All About Balance

In mammalian cells, the small ubiquitin-like modifier (SUMO) family contains four isoforms (SUMO1, SUMO2, SUMO3, and SUMO4). SUMO2 and SUMO3 are almost identical, with only a difference in three amino acid residues. SUMO1 shares 48% identity with SUMO2/3¹. SUMO4 is about 85% identical to SUMO2/3, but it is unclear whether SUMO4 can be conjugated to substrates². Similar to ubiquitination, SUMOylation requires a three enzymes system (E1, E2, and E3) to conjugate SUMO covalently to target substrates. Briefly, SUMO is first activated by the SUMO E1 activating heterodimeric enzyme SAE1/SAE2 by adenylation in an ATP-dependent reaction. The activated SUMO is then transferred to the SUMO E2 conjugating enzyme UBC9 and finally conjugated to a target protein by a SUMO E3 ligase (e.g., PIAS family members, Ran binding protein 2). The covalently linked SUMO can be removed by sentrin-specific proteases (SENPs), a process known as deSUMOylation³ (Fig. 1). SUMOylation is an essential post-translational modification (PTM) that regulates the activity, subcellular localization, stability, and functions of target proteins and thereby modulates almost all major cellular pathways⁴. Therefore, it is not surprising that many diseases are associated with dysregulation of SUMOylation. In this newsletter, the roles of SUMOylation/deSUMOylation in cancer are discussed.

SUMOylation in Cancer Development

Cancer occurs when cells grow abnormally. Many regulatory proteins involved in cell cycle progression are tightly regulated by PTMs, and SUMOylation has been identified as one of the major players in cell cycle progression and cancer regulation⁵. Overexpression of components of the SUMO conjugation pathway supports tumor growth. For example, the oncoprotein Myc activates the transcription of SUMO-activating enzyme E1 (SAE1)⁶. SAE1 and its partner SAE2 are important in supporting Myc-driven tumorigenesis. Depletion of SAE2 greatly reduces levels of SUMO1- or SUMO2/3-modified proteins, leading to decreases in Myc-dependent breast cancer growth and clonogenicity⁷. Other studies have reported that the SUMO E2-conjugating enzyme UBC9 is important in early stages of cancer development⁸ and is overexpressed in lung, primary colon, and prostate cancers. Interestingly, UBC9 levels are downregulated in metastatic breast, lung, and prostate cancers compared with corresponding normal tissues and primary tumors⁹. In viral (HPV)-mediated head and neck tumorigenesis, UBC9 levels

are upregulated through autophagic processes⁸. In astrocytic brain tumors, upregulation of UBC9, SUMO1-, and SUMO2/3-conjugated proteins promotes tumor growth. Blocking SUMO1-3 conjugation in glioblastoma cells impairs DNA synthesis, cell proliferation, and clonogenicity due to DNA double-strand damage and G2/M cell cycle arrest¹⁰. Further, the SUMO E3 ligase PIAS1 is involved in tumorigenesis¹¹. PIAS1 is amplified in prostate cancer where it promotes cell proliferation by suppressing p21¹². PIAS1 is highly expressed in Myc-driven B-cell lymphomas. It stabilizes Myc in a SUMOylation-dependent manner. PIAS1 also promotes Myc phosphorylation at S62, leading to stabilization and upregulation of Myc and therefore its transcriptional activity¹³.

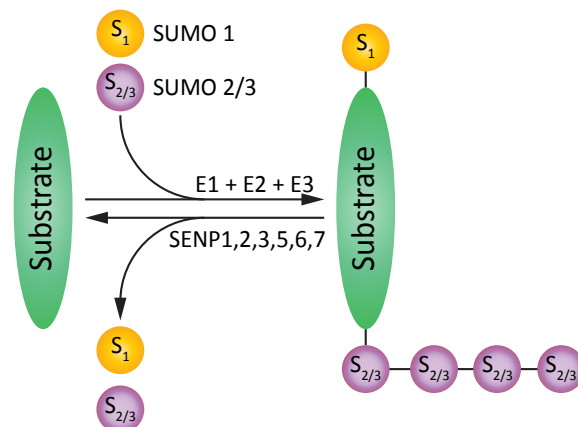


Figure 1. An outline of SUMOylation and deSUMOylation processes.

DeSUMOylation in Cancer Development

DeSUMOylation by SENPs maintains SUMO homeostasis in cells. However, abnormal activity in deSUMOylation also promotes tumorigenesis¹⁴. Overexpression of SENP1 is associated with prostate cancer development. Analysis from prostate cancer specimens also reveals that SENP1 expression directly correlates with prostate cancer aggressiveness and recurrence¹⁵. SENP1 is upregulated in prostate cancer cells treated with androgen and/or interleukin-6. Upregulation of SENP1 enhances androgen-dependent transcription and c-Jun-dependent transcription; both important for prostate cancer development¹⁶. Interestingly, blocking SENP2 by siRNA enhances hepatocellular carcinoma growth through increased β -catenin stability¹⁷. Upregulation of



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SENP3 enhances epithelial ovarian cancer progression, possibly by inhibiting p53 transcriptional activity and the expression of p21¹⁸. Overexpression of SENP3 is associated with the differentiation of oral squamous cell carcinoma¹⁹. Upregulation of SENP5 promotes growth in osteosarcoma cells²⁰ and enhances tumorigenesis in hepatocellular carcinoma²¹. SENP6 is overexpressed in hepatocellular carcinoma tissues. Silencing of SENP6 by shRNA induces growth inhibition and radio-sensitization in hepatocellular carcinoma cell lines²². In breast epithelia, overexpression of the long SENP7 splice variant promotes breast epithelial-mesenchymal transition²³.

Targeting SUMOylation Pathways in Cancer

SUMOylation pathways have become a potential therapeutic target in cancer. For example, the small molecule STE inhibits SUMO E1-activating enzyme activity, impairing SUMOylation and inhibiting lung cancer cell growth. This is particularly important in Myc-driven cancer since its survival is highly dependent on SUMO E1 activity²⁴. Another study has reported that ginkgolic acid binds directly to SUMO E1 and inhibits SUMOylation. Ginkgolic acid treatment inhibits the growth of NOTCH1-driven breast epithelial cells, suggesting a potential effect of ginkgolic acid treatment in NOTCH1-driven breast cancer²⁵. Several chemotherapeutic drugs used in the treatment of acute myeloid leukemia induce the formation of reactive oxygen species, which inhibits the interaction between the SUMO E1-activating enzyme and SUMO E2-conjugating enzyme, resulting in reduction of tumor growth²⁶. Arsenic trioxide, a drug used in traditional Chinese medicine, promotes SUMOylation and subsequent degradation of the PML and PML-RAR α fusion oncoprotein, which is responsible for the development of acute promyelocytic leukemia²⁷.

Summary

PTMs such as acetylation, phosphorylation, ubiquitination, and SUMOylation regulate protein structure, subcellular localization, and activity in all major cellular pathways. Various human diseases, including cancer, heart failure, neurodegeneration, and brain ischemia/stroke are associated with dysregulation in SUMOylation³. However, how SUMOylation/deSUMOylation interaction (i.e., cross-talk) with other PTMs contributes to pathological conditions remains unexplored. Cytoskeleton offers several Signal-Seeker™ PTM Detection Kits to assist scientists in the identification and evaluation of endogenous levels of PTM-modified proteins.

PTM Antibodies, Beads, Etc

Kit or Affinity Beads	Type	Size	Cat. #
Acetyl-Lysine Antibody Mouse Monoclonal (7B5A1)	MAB	2 x 100 ul 1 x 25 ul	AAC02 AAC02-S
Acetyl-Lysine Antibody Mouse Monoclonal (19C4B2.1)	MAB	2 x 100 ul 1 x 25ul	AAC03 AAC03-S
Acetyl-Lysine-HRP Antibody Mouse Monoclonal (19C4B2.1)	MAB	1 x 100 ul 1 x 25 ul	AAC03-HRP AAC03-HRP-S
Acetyl-Lysine Affinity Beads	Beads	4 x 500 ul	AAC04-beads
Phosphotyrosine Affinity Beads	Beads	4 x 330 ul	APY03-beads
SUMO 2/3 Affinity Beads	Beads	2 x 400 ul	ASM24-beads
Ubiquitin Affinity Beads	Beads	40 reactions	UBA01-beads
Control for IgG Beads	Beads	10 reactions	CIG01-beads
Control for Ubiquitin Affinity Beads	Beads	10 reactions	CUB02-beads

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Signal Seeker™ Kits

Kit or Affinity Beads	Type	Reactions	Cat. #
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		10	BK163-S
Signal-Seeker™ Phosphotyrosine Enrichment Kit	Kit	30	BK160
		10	BK160-S
Signal-Seeker™ Ubiquitin Enrichment Kit	Kit	30	BK161
		10	BK161-S
Signal-Seeker™ SUMO 2/3 Enrichment Kit	Kit	30	BK162
		10	BK162-S