Review

Recent Progress of DeSUMOylation in Biological Processes: A Mini Review

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Post-translational modifications to proteins are essential mechanisms for controlling functions of proteins and subsequently for regulating cell fate. SUMO modification (SUMOylation) has emerged as a critical regulatory pathway in cellular function and biological processes. DeSUMOylation (removal of SUMO conjugation) by members of SUMO-specific proteases (SENPs) family makes SUMO modification highly dynamic. In this mini-review, we briefly introduce the current knowledge regarding the regulatory pathway of deSUMOylation and focus on the recent progress of functions of SENPs in biological progresses.

[N A J Med Sci. 2012;5(2):71-77.]

Key Words: *SUMO, deSUMOylation, SENP*

INTRODUCTION

The molecular basis of biological activity has recently been challenged by the recognition of additional mechanisms. Post-translational modifications are essential and/or required mechanisms for controlling functions of proteins and subsequently for regulating cell fate and normal cell physiology. Post-translational modification of proteins involving conjugation members of the small ubiquitin-related modifier (SUMO) family, which was discovered in 1997 and is highly conserved from yeast to humans and in plants, has been shown to regulate and influence diverse cellular processes and signaling pathways, including cancer development, progression, and metastasis,[1,2] cell cycle regulation and apoptosis,[3-5] chromosome segregation,[6,7] DNA repair,[8,9] formation of sub-nuclear structures,[10,11] nuclear-cytosolic transport,[12,13] protein stability and degradation,[14-16] and transcriptional regulation and nuclear body assembly.[17-19]

In mammals, four SUMO isoforms (SUMO1, SUMO2, SUMO3, and SUMO4) are encoded by distinct genes. SUMO1 has approximately 50% identity to either the closely related SUMO2 or SUMO3.[20,21] SUMO2 and SUMO3 share approximately 95% sequence homology. SUMO4, very similar to SUMO2/3, is associated with susceptibility to type 1 diabetes mellitus.[22] In contrast to SUMO1, SUMO2 and SUMO3 contain a conserved consensus SUMOylation site in their N-terminal regions, therefore efficiently form polymeric chains.[23] Recent studies demonstrate that SUMO chains may function in facilitating the recruitment of ubiquitin ligases, which subsequently targets poly-ubiquitinated and/or poly-SUMOylated proteins for proteasomal degradation.[24-26]

Received 01/25/2012; Revised 02/11/2012; Accepted 02/15/2012
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Recent data suggest some selectivity in the SUMO1 and SUMO2/3 modification of proteins.[20] Although the consequences of selective conjugation of different SUMO family isoforms remain largely undiscovered, the functional effects of protein modification by SUMO2 and/or SUMO3 can be distinguished from that of SUMO1 in the control of transcriptional activity.[27]

Despite limited sequence identity, SUMO proteins and ubiquitin have similar 3D structure, share common ancestry, and use an enzymologically parallel pathway of conjugation. Newly translated SUMO proteins are processed by sentrin/SUMO specific cysteine proteases (SENPs) to remove C-terminal residues in SUMO and to expose a conserved di-glycine motif, generating active SUMO proteins.[28] The SENP isoforms exhibit different affinity for the SUMO proteins in this endopeptidase activity. After this initial cleavage step, SUMO is then activated by the formation of a thioester bond between the carboxy-glycine residue of SUMO and the cysteine residue of the heterodimeric E1-activating enzyme SAE1/SAE2 in an ATP-dependent manner.[29] This activated thioester-linked SUMO is then transferred from E1 enzyme to the SUMO-specific E2-conjugating enzyme Ubc9, which in turn recognizes specific substrates and catalyzes the formation of an isopeptide bond between SUMO and the lysine residue of the target substrate.[29,30] SUMO conjugation can be preformed directly by E2 enzyme alone or facilitated by SUMO E3 ligases, such as RanBP2 and members of the protein inhibitor of activated STAT (signal transducers and activators of transcription) (PIAS) family.[31-33] Covalent modification of proteins by SUMO is reversible and all SENP proteins of family exhibit isopeptidase activity to cleave the isopeptide bond between the lysine residue of the target substrate and the glycine residue of SUMO (**Figure 1**). Although the majority target proteins for SUMO modification are nuclear proteins, several

lines of evidence from recent studies suggest that cytosolic as well as intergral membrane proteins (plasma and mitochondrial membranes) are SUMOylated [34-36] and that SUMOylation exerts important and expanded regulatory roles.

In mammals, six SENP proteins (SENP1, SENP2, SENP3, SENP5, SENP6, and SENP7) have been identified and well characterized. SENP4 was later found to be identical to SENP3. Generally, N-terminus of SENP determines paralogue specificity, while C-terminus is a catalytic domain.[37] Each SENP protein has different substrate specificities and cellular localizations. For example, SENP3, SENP5, SENP6, and SENP7 favor deconjugating SUMO2 and SUMO3 than SUMO1; however, SENP1 and SENP2 can deSUMOylate target proteins modified by any of the 3 SUMO proteins. For localization, SENP3 and SENP5 are mainly localized in the nucleolus, while SENP1, SENP6, and SENP7 are mainly distributed in the nucleoplasm. A recent study indicates that knockdown of SENP7 expression leads to the accumulation of SUMO2, SUMO3, and promyelocytic leukaemia (PML) proteins.[37-40] Several lines of evidence demonstrate that knockout of either SENP1 or SENP2 with excessive SUMO modification results in embryonic lethality.[41-43] Under normal physiological conditions, only a small amount of the total proteins is SUMOylated (<10%). Therefore, balancing SUMOylation and deSUMOylation (by SENP proteins) is essential for maintaining normal physiological conditions and are critical for normal cellular events.

This mini-review focuses on the roles and functions of SENP proteins for recent progress of deSUMOylation in biological processes. The detailed functions of SENP-mediated deSUMOylation in cancer development and progression,[44,45] in yeasts,[46] and in plants[47] have been reviewed elsewhere.

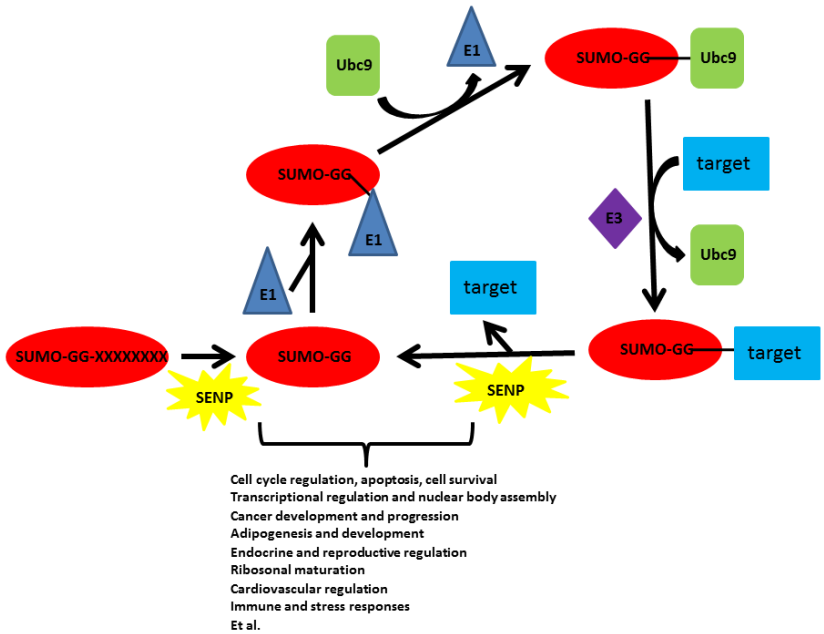

Figure 1. SUMOylation-deSUMOylation cycle. Newly translated SUMO proteins are processed by SENPs to remove C-terminal residues in SUMO and to expose a conserved di-glycine motif, generating active SUMO proteins. After this maturation process, SUMO is then activated by the formation of a thioester bond between the carboxy-glycine residue of SUMO and the cysteine residue of the heterodimeric E1-activating enzyme SAE1/SAE2 in an ATP-dependent manner. This activated thioester-linked SUMO is then transferred from E1 enzyme to the SUMO-specific E2-conjugating enzyme Ubc9. SUMOylation can be done directly by E2 enzyme alone or facilitated by SUMO E3 ligases. DeSUMOylation is processed by SENPs and free SUMO may be recycled for another SUMOylation cycle.

DESUMOYLATION IN RECENT BIOLOGICAL PROCESSES

Apoptosis, Cell Cycle, and Cell Survival

Apoptosis

Cell signaling pathways determine and control cell cycle progression, cell growth, cell differentiation, cell survival, and tumorigenesis. Apoptosis is an important physiological form involved in many biological processes, including organogenesis, aging, and diseases. SUMO conjugation and deconjugation also regulate the molecular mechanisms of apoptosis. For example, HIPK1, a serine/threonine-protein kinase, is involved in transcription regulation and TNF-mediated cellular apoptosis. HIPK1 can be SUMOylated in the nucleus. In resting cells, SENP1, localized in the cytoplasm, is complexed with antioxidant protein thioredoxin. TNF induction releases the association between

SENP1 and thioredoxin, resulting in SENP1 nuclear translocation, which deSUMOylates HIPK1 and leads to an enhanced apoptosis.[48]

DNA repair

Cells require DNA repair system to correct damages to the DNA molecules in order to survive. Regulation of DNA repair also requires balanced SUMOylation and deSUMOylation processes. In normal physiological condition, SENP6 binds to RPA70, a component of replication protein A complex, and keeps RPA70 in a hypoSUMOylated state during the S phase. Upon induction of replication stress, SENP6 no longer binds to RPA70, resulting in hyperSUMOylated RPA70, which recruits specific mediators to the DNA damage foci to facilitate DNA repair.[49]

Cell division

Kinetochore assembly is essential for cell division during mitosis and meiosis. Normally, RNF4, an ubiquitin ligase, targets poly-SUMOylated proteins for proteasomal degradation, including CENP1 complex, which is required for kinetochore composition. A recent study has been shown that SENP6 plays an important role in spindle assembly and metaphase chromosome congression. First, cells lacking SENP6 proteins show defects in cell division. Secondly, overexpression of SENP6 stabilizes CENP1 complex by reducing proteasomal degradation.[50] SENP2 also deconjugates SUMOylated Aurora-B, resulting in decreased phosphorylation of Aurora-B and impaired cell division.[51] Therefore, fine balanced SUMOylation and deSUMOylation processes control cell division.

Proliferation, senescence and genome integrity

Both proliferation and senescence are regulated by SUMO conjugation and deconjugation. For example, SENP1 repression by RNA interference results in global increase in SUMOylated proteins and in the number of nuclear PML bodies as well as p53-mediated transcription activity, leading to premature senescence.[52] Therefore, deSUMOylation by SENP1 is important for proliferation of normal human cells. Since its discovery in 1979, p53 is the most crucial factor in cell cycle regulation and genome maintenance. Recent studies suggest that genome integrity and cell cycle regulation by p53 also require balanced SUMOylation and deSUMOylation. For example, it has been known that SENP2 interacts with SUMOylated Mdm2 and regulates its SUMO conjugation at the PML body in the nucleus. DeSUMOylation of Mdm2 by SENP2 permits Mdm2-p53 binding in the cytoplasm and then ubiquitination of p53, leading to p53 proteasomal degradation. Therefore, SENP2 regulates p53 activity through modulation of Mdm2.[53] Moreover, a recent study has demonstrated that SENP3 attenuates Mdm2-mediated p53 ubiquitination and degradation.[54] Overall, deSUMOylation by SENP proteins plays an essential role in cell cycle regulation and cell survival.

Transcriptional Regulation and Nuclear Body Assembly

The majority of SUMO substrates identified so far are localized in the nucleus and SUMOylation mainly regulates transcriptional activities of target proteins as well as nuclear body assembly. For example, SENP proteins regulate transcriptional activities of RCOR1 (CoREST),[55] Elk1,[56] BZLF1,[57] and PML.[58] PML, a transcription factor and tumor suppressor, can be SUMOylated and is required for formation and regulation of PML nuclear body. It has been shown that SENP1 activation by IL6 removes SUMO from PML, leading to modulation of STAT3 activation.[58] A recent study also shows that SUMO-conjugated PML is a substrate of SENP6. Depletion of SENP6 results in hyper-SUMOylated PML proteins and increased size of PML nuclear body.[59] These results suggest that SENP proteins regulate PML activity and nuclear body formation.

Cancer Development and Progression

SUMOylation also involves in cancer development and progression. Recent progress of SENP-mediated deSUMOylation in prostate and colon cancers has been reported and thus we briefly summarize here. Androgen receptor (AR) is the main target for prostate cancer treatment and therapy. AR has been shown to be SUMOylated at lysine residues 386 and 520. Studies have shown that SENP1 and SENP2 are efficient in cleaving SUMOylated AR. DeSUMOylation by SENP1 and SENP2 also enhances AR-mediated transcriptional activity in promoter assays. Moreover, in prostate cancer cells, overexpression of SENP1, but not SENP2, increases the transcriptional activity of endogenous AR. Knockdown SENP1 expression in LNCaP prostate cancer cells attenuates cell growth.[60] Therefore, SENP1 is essential for prostate cancer proliferation and growth. The mechanisms that SENP1 induces prostate cancer cell growth could be due to HIF1α activation and stabilization, leading to increased VEGF and cyclin D1 levels and in turn increased angiogenesis, eventually resulting in cell growth.[61] Recent studies have shown that SENP1 is over-expressed in most of colon cancer tissues. SENP1 deletion inhibits cell growth by up-regulating CDK inhibitors, such as p16 and p21.[62] Overall, SENP proteins might play a significant role in cancer growth and be a suitable target for cancer treatment and therapy.

Adipogenesis and Development

DeSUMOylation also plays a critical role in the control of normal development, erythropoiesis, adipogenesis and adipocyte differentiation. For example, Deletion of *Xenopus* SENP3 causes accumulation of hyper-SUMOylated species, resulting in developmental defects in embryos.[63] Studies have shown that induction of adipocyte differentiation triggers SENP2 expression. Knockdown of SENP2 reduces adipogenesis by inhibiting PPARγ and C/EBP signaling pathways. Furthermore, in mouse model, adipogenesis of preadipocytes requires the presence of SENP2.[64] Another example is that global deletion of SENP1 causes anemia and embryonic lethality due to erythropoiesis defects. Further analysis shows that the defects are mainly due to down-regulated GATA1 and GATA1-dependent genes in fetal liver.[65] Therefore, SENP1 is required for promoting GATA1 activation by deSUMOylating GATA1 and subsequent erythropoiesis. A recent study has demonstrated that SUMO

proteins are involved in the stress response during spermatogenesis;[66] however, it is unclear whether SENP proteins are directly involved during normal spermatogenesis.

Endocrine and Reproductive System

SUMO modification has been shown to play an essential role in germ cell development in the testis and male reproduction. Retinoic acid and its receptor are involved in SUMOylation-mediated processes. All-trans retinoic acid (ATRA) induces SUMO2 modification of retinoic acid receptor α (RARA) at lysine residues 166 and 171. However, without ligand stimulation, only lysine 399 is SUMOylated by SUMO2. A further study has shown that lysine 399 is critical for RARA nuclear trafficking. However, SUMOylation of lysines 166 and 171 inhibits RAPA nuclear localization. Interestingly, SENP6 is able to bind to wild-type RARA but not K399R mutant.[67] Moreover, retinoic acid also modulates the subcellular localization of SUMO2 and SUMO3.[68] Therefore, both SUMOylation and deSUMOylation are critical for RARA activity in Sertolic and germ cells in the testis. Ectopic ACTH syndrome is mainly characterized by tumoral cortisol resistance. Recent studies have demonstrated that SMRT, a major nuclear corepressor expressed in ACTH-secreting thymic carcinoids, participates in the negative feedback loop of dexamethasone-mediated suppression of proopiomelanocortin. In dexamethasone-resistant cells, SMRT is heavily SUMOylated. Interestingly, overexpression of SENP proteins increases suppression of proopiomelanocortin by dexamethasone partly due to reduced interaction of SMRT and HDAC3. These results suggest that targeting SUMOylation pathway might be a suitable therapeutic approach for ectopic ACTH syndrome patients.[69] The pathways critical for syncytiotrophoblast formation and synthesis by trophoblast fusion are essential for pregnancy maintenance. GCM1 is a transcription factor that is necessary for trophoblast fusion and placental development. SUMO modification of GCM1 on lysine 156 reduces its activity. Upon cAMP stimulation, GCM1 is phosphorylated and subsequently recruits SENP1, leading to deSUMOylation of GCM1, resulting in transcriptional activation of GCM1. These results indicate that the interplay between phosphorylation and SUMOylation/deSUMOylation is critical for placental cell fusion.[70] SUMOylation also plays a role in the regulation of insulin secretion. A recent study has shown that SUMO1 impairs glucose-induced insulin secretion by blocking β-cell exocytosis to Ca^{2+} signaling. Interestingly, overexpression of SENP1 rescues exocytosis and deletion of SENP1 further impairs exocytosis.[71] Overall, deSUMOylation by SENP1 is critical for glucose-dependent insulin secretion.

Ribosomal Maturation

SUMOylation-deSUMOylation cycle also participates in rRNA processing and ribosome maturation. NPM1 is involved in diverse processes such as ribosome biogenesis and centrosome duplication. NPM1 can be SUMOylated by SUMO2 resulting in interference with 28S rRNA maturation. This interference can be rescued and relieved by SENP3, suggesting that deSUMOylation of SUMO2 from NPM1 by SENP3 is critical for rRNA maturation.[72] SENP3 is also required for maturation of 60S ribosomal subunit. Knockdown SENP3 prevents PELP1-TEX10-WDR18 complex recruiting to 60S particles thereby reducing ribosome maturation.[73] LAS1L is another nucleolar protein required for maturation of 60S subunit. A recent study has shown that LAS1L interacts with PELP1-TEX10-WDR18 complex along with SENP3 to form a nucleolar complex that co-fractionates with 60S subunit. SENP3 is also required for nucleolar localization of this complex.[74] These results indicate that SENP3 is important for ribosome biogenesis.

Cardiovascular System

Recent studies also suggest the link between SUMOylation/deSUMOylation and cardiovascular function. TRPM4, a calcium-activated non-selective cation channel that mediates membrane depolarization, is involved in progressive familial heart block. A recent study shows that Glu7Lys (E7K) mutation of TRPM4 reduces its deSUMOylation, resulting in impaired endocytosis due to hyper-SUMOylation of the channel. [75] PPARγ also plays a role in atherosclerosis. A recent study shows that deSUMOylation of PPARγ at lysine 107 significantly inhibits proliferation and migration of vascular smooth muscle cells and also reduces neointimal formation after balloon injury.[76] These results suggest that deSUMOylation is critical against atherosclerosis. More studies are needed to further investigate which SENP proteins are directly involved in these processes. A global knockout of SUMO1 in mice results in congenital heart diseases. A recent report demonstrates that enhanced deSUMOylation by SENP2 overexpression in the hearts of mice promotes congenital heart defects and cardiac dysfunction,[77] suggesting that a balanced SUMOylation-deSUMOylation pathway is critical for proper cardiac function.

Nervous System

SUMOylation targets are also present in nervous system. Recent studies have shown that kainate receptor subunit GRIK2, an ionotropic glutamate receptor that functions as an excitatory neurotransmitter at many synapses in the central nervous system, is a SUMO substrate. SUMOylation of GRIK2 regulates endocytosis of kainate receptor and subsequent synaptic transmission. However, deSUMOylation by SENP1 prevents endocytosis of kainate receptor.[78] Interestingly, kainite receptor-mediated excitatory post-synaptic currents are reduced by SUMOylation and increased by SENP1, suggesting SUMOylation-deSUMOylation pathway regulates synaptic transmission and function. The central nervous system uses oxygen and glucose as main energy sources. It has been shown that glucose and oxygen deprivation induces SUMO conjugation to substrates in the central nervous system. However, glucose and oxygen deprivation also trigger SENP1 synthesis. Further studies have shown that SENP1 increases glucose and oxygen deprivation-induced cell death,[79] suggesting that SUMOylation plays a protective role in neurons after oxygen and glucose deprivation. However, more studies are indeed needed to dissect the roles of SENP proteins in cell injury from oxygen and glucose deprivation.

Immune System and Stress Response

Toll-like receptors (TLRs) are important initiators and sensors for inflammatory response and tissue damage. It has been shown that SUMOylation of liver X receptors suppresses TLRs-induced transcriptional activity by preventing clearance of NCoR complex. CORO2A, a component of NCoR complex, has been shown to interact with SUMOylated liver X receptors, resulting in preventing actin recruitment. A further study has shown that deSUMOylation of liver X receptors by SENP3 releases CORO2A, leading to NCoR departure, resulting in enhanced TLRs-induced transcriptional activity.[80] These results suggest that deSUMOylation plays an important role in controlling homeostasis and immunity. SUMOylation-deSUMOylation cycle also participates in regulating innate immunity and viral infection. IRF3 mediates interferon-stimulated promoter activation and functions as a molecular switcher for antiviral innate immunity. A recent report shows that SENP2 removes SUMO conjugation from IRF3 and promotes IRF3 for ubiquitination and subsequent proteasomal degradation. Moreover, in SENP2-deficient cells, INFβ is activated and viral replication is reduced,[81] suggesting that SUMOylation/deSUMOylation and ubiquitination play a critical role in regulating innate immunity. DeSUMOylation also plays a role in response to genotoxic stress and cell injury. NEMO, NF-κB essential modulator, is critical for NF-κB activation and pivotal for immunity and oncogenesis. A recent report suggests that SENP2 associates with NEMO, deSUMOylates NEMO, and subsequently inhibits NF-κB activation, resulting in lower resistance to cell death induced by DNA damage.[82] In H_2O_2-induced oxidative stress, SENP1 has been shown to impair SUMO1-mediated phosphorylation of JNK and reduce cell death.[83] These results demonstrate that deSUMOylation might play a protective role in oxidative stress-induced cell injury. Moreover, SUMOylation also plays a role in the development of the immune system, such as lymphoid development. A recent report has shown that SENP1 is critical for the development of early T and B cells and regulates the functions of STAT5, a key regulator of lymphoid development.[84] Deletion of SENP1 results in accumulated SUMOylated STAT5, which blocks its acetylation and impairs downstream signaling pathways.[84] Therefore, SENP1 is essential for early lymphoid development during embryonic development.

Methodology and Inhibitor Design

Since deSUMOylation by SENP proteins plays critical roles in many diverse biological processes, developing modern techniques to detect the activity of SENP proteins and also designing novel inhibitors for SENPs are indeed necessary. For example, ginkgolic acid has been shown to block SUMOylation by interfering E1-SUMO formation.[85] A sensitive enzyme-based SUMO-CHOP reporter assay could be used to determine Km of SENPs and to characterize inhibitors of SENPs.[86] Forster resonance energy transfer (FRET)-based and time resolved (TR)-FRET-based assays could be used to analyze SENP activities.[87-89] All SENP proteins share a similar C-terminal domain with the catalytic triad (active site) (His-Asp-Cys) and 3D structure in the catalytic domain.[90-95] Mutagenesis studies reveal that disruption of catalytic triad abolishes maturation processing and deSUMOylation activities of SENP proteins.[94,96] In SENP6 and SENP7, the most divergent family members of SENP proteins, there is an additional loop insertion (with sequence P-P-P-P-T/A-K) that separates the conserved catalytic domain.[38,40] It has been shown that this additional loop may play an important role for SUMO2/3 isoform specificity of SENP6/7.[40] Searching for novel inhibitors for SENP proteins is also making progress recently. For example, inhibitors and active site probes containing aza-epoxide and acyloxymethyl ketone (AOMK) groups have been tested and shown effectively inhibiting human SENP isoforms.[97] Another example is the group of benzodiazepine-based SENP1 inhibitors.[98] One group of benzodiazepine scaffold inhibitors exhibits strong inhibitory activity with IC_{50} around 9.2 nM. Therefore, for future therapeutic target purpose, further studies are indeed necessary to explore searching for more potent SENP inhibitors by synthesis and designing methods.

CONCLUSIONS AND PERSPECTIVES

The function and activity of SENP proteins make SUMOylation process a highly dynamic post-translational protein modification. From the recent studies, we can assure that SUMOylation and deSUMOylation cycle regulates many diverse biological processes including transcription, cell cycle regulation, apoptosis, cell survival, organogenesis, development, immune and stress responses, ribosomal maturation, cancer initiation and progression. Keep in mind that deSUMOylation by SENPs may also play a critical role in regulating interplay and crosstalk among post-translational modifications, such as SUMOylation, phosphorylation, acetylation, methylation, and neddylation. Indeed, we need more studies to complete the signaling networks regulated by SUMOylatgion-deSUMOylation cycle to get insight into future drug design to overcome a variety of diseases.

ACKNOWLEDGEMENTS

This work is supported by Mercer University Seed Grant (W.H.Y.).

CONFLICT OF INTEREST

No conflict of interest.

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