SUMO junction—what's your function? New insights through SUMO-interacting motifs

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The small ubiquitin-like modifier, SUMO, can be covalently linked to specific proteins and many substrates carrying this modification have been identified. However, for some proteins, the role that SUMO modification imparts remains obscure. Our understanding of SUMO biology and function has been significantly advanced by the recent discovery of proteins and protein domains that contain SUMO-interacting motifs (SIMs), which interact non-covalently with SUMO. Unlike the motifs and domains that mediate ubiquitin binding, the diversity of SIMs seems limited. Nevertheless, SIMs have already increased our understanding of how SUMO affects DNA repair, transcriptional activation, nuclear body formation and protein turnover. This review takes a detailed look at how SIMs were identified, how they specifically bind to SUMO, their crucial roles in multi-step enzymatic processes, and how they direct the assembly and disassembly of dimeric and multimeric protein complexes.

Keywords: SUMO; SIM; ubiquitin; SBM; SBD

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Introduction

The small ubiquitin-like modifier (SUMO) protein can be covalently attached to specific eukaryotic protein targets. There are at least three SUMO isoforms (SUMO1,-2,-3) in mammalian cells but only one in *Saccharomyces cerevisiae* (Smt3). Many SUMO-modified proteins reside in the nucleus but cytosolic SUMO targets have also been identified. Sumoylation occurs in a stepwise and regulated manner that involves a cascade of SUMO-specific enzymes (reviewed by Johnson, 2004; Kerscher *et al*, 2006). Of particular interest in this respect are SUMO ligases and proteases. SUMO ligases, including those of the conserved protein inhibitor of activated STAT (PIAS) family, ensure that the appropriate targets are modified with SUMO. By contrast, SUMO proteases remove SUMO from their target proteins and are responsible for ensuring correct SUMO conjugation by processing SUMO precursors and exposing their carboxy-terminal di-glycine motif. Ultimately, SUMO attachment modulates the functional properties of a protein, such as its localization, activation, interactions and half-life.

Interestingly, SUMO also shares some substrates with ubiquitin, creating further opportunities to direct protein function (reviewed by Ulrich, 2005).

The first SUMO-modified protein to be identified, Ran GTPase-activating protein 1 (RanGAP1), was reported approximately ten years ago (Mahajan *et al*, 1997; Matunis *et al*, 1996). It had just been accepted that SUMO could be covalently attached to a subset of cellular proteins when additional substrates were identified that interacted non-covalently with SUMO. For example, three studies detailed the non-covalent interaction of human Rad51 and Rad52 with SUMO (Li *et al*, 2000; Shen *et al*, 1996a,b). Since then, two-hybrid assays have proven to be a convenient tool to differentiate between covalent and non-covalent interactions with SUMO. Proteins that can still interact with SUMO even in the absence of the C-terminal di-glycine motif are good non-covalent-interactor candidates. By using this approach, many yeast and mammalian SUMO-interacting proteins and their SUMO-interacting motifs (SIMs, also known as SUMO-binding domains (SBDs) or motifs (SBMs)) have been discovered (Hannich *et al*, 2005; Hecker *et al*, 2006). This review details how SIMs were identified, examines the important structural features of SIMs, and finally discusses some intriguing examples of how SIMs modulate the function of several proteins involved in DNA replication, nuclear body formation and the response to DNA damage.

Defining a SUMO-interacting motif

Minty and co-workers were the first to report specific SUMO-interacting proteins that contain conserved SIMs (Minty *et al*, 2000). By using a two-hybrid approach, they observed that certain proteins were able to interact with the sumoylated version of p73, a member of the p53 family. Comparing the sequences of these proteins, the authors noticed a common Ser-X-Ser (SXS) sequence, in which X is any amino acid, flanked by a hydrophobic core on one side and acidic amino acids on the other. This SXS sequence also interacted strongly with SUMO in a two-hybrid assay. The two serines and the hydrophobic core residues were required for SUMO interaction. However, a second study published approximately four years later disputed the importance of these serine residues (Song *et al*, 2004). By probing the interaction of SUMO with SIM-containing peptides, Song and co-workers instead suggested that it was the hydrophobic core, with the consensus Val/Ile-X-Val/Ile-Val/Ile (V/I-X-V/I-V/I), which allowed SUMO to bind to SIMs. Several proteins contain this motif, including the SUMO

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ligases PIASX and Ran binding-protein 2 (RanBP2/Nup358), and the SUMO-activating enzyme subunit Uba2/Sae2. Subsequently, a possible SIM was identified in yeast with similar characteristics to that defined in mammalian cells—that is, a hydrophobic core and flanking acidic residues (Hannich *et al*, 2005; Hecker *et al*, 2006). It became evident that the hydrophobic core, consisting of 3–4 aliphatic residues, was indeed often juxtaposed to a negatively charged (acidic) cluster of amino acids. We now know that the hydrophobic core is a quintessential component of the SIM.

How do SUMO-interacting motifs bind to SUMO?

SIMs are characterized by a loose consensus sequence and variants are plentiful. The section below describes the variant and invariant features of SIMs and how different SUMO isoforms become specifically bound to their target proteins.

SUMO-interacting motifs are hydrophobic. The structure of SUMO1 in complex with a SIM-containing PIASX peptide revealed the interactions between individual hydrophobic and aromatic amino acids of SUMO and the SIM-containing peptide (Song *et al*, 2005). For both SUMO1 and SUMO2, these residues are arranged in a SIM-binding groove of the SUMO molecule (Fig 1A,B). The SIM peptide assumes an extended configuration and is embedded in the groove formed between the α -helix and the β -strand of SUMO1. It has been proposed that SIMs assume an intramolecular β -sheet structure with the β 2 strand of SUMO. From nuclear magnetic resonance and crystal structures, several crucial hydrophobic residues of SUMO1 such as phenylalanines, valines and leucine—specifically, Phe 36, Val 38 and Leu 47—have been found to interact with SIMs (Fig 1B; Baba *et al*, 2005; Hecker *et al*, 2006). A single amino-acid change in the hydrophobic core of a SIM can greatly reduce its interaction with SUMO. Correspondingly, mutating Phe36 of SUMO1 does not significantly alter its structural integrity but decreases its interaction with SIMs.

Clusters of charges. Many, but certainly not all, SIM-containing proteins have a cluster of acidic amino-acid residues—that is, aspartic and glutamic acid—juxtaposed with the hydrophobic core (Fig 2B). Electrostatic interactions promoted by these residues have an important role in the affinities, orientation and functionality of SIM–SUMO associations (Hecker *et al*, 2006; Song *et al*, 2005). Similarly, serine and threonine residues can be found adjacent to many hydrophobic SIM domains. It has been proposed that phosphorylation of these residues might be one way to introduce negative charges into SIMs. These residues could then interact with lysine residues, such as Lys 39, of SUMO1 (Hecker *et al*, 2006). This conserved lysine is part of the hydrophobic groove in all three mammalian SUMO isoforms.

A choice of orientation. There is variability in the composition of the hydrophobic core as well as in the placement of charged amino acids (Fig 2A,B). Curiously, this allows SIMs to bind SUMO in either a parallel or an anti-parallel orientation with respect to the β 2 strand of SUMO (Fig 2C). For example, SUMO binding to the SIMs in thymine DNA glycosylase (TDG) and RanBP2 occurs in an anti-parallel orientation, whereas SUMO binding to a PIAS protein-derived SIM occurs in parallel (Baba *et al*, 2006; Reverter & Lima, 2005; Song *et al*, 2005). It is possible, therefore, that the orientation of the hydrophobic core together with its charge distribution dictates

Fig 1 | Determinants of the SUMO-interacting motif. (A) Model of the β -grasp fold of the small ubiquitin-like modifier. Indicated are the β 2 strand and α 1 helix of SUMO and the groove formed between them. (B) β 2 strand and α 1 helix of aligned SUMO isoforms and ubiquitin (Huang *et al*, 2004). Conserved residues of SUMO1 that command hydrophobic interactions with SIMs are shown in green (Baba *et al*, 2005; Hecker *et al*, 2006). Underlined in bold are residues that interact with protein inhibitor of activated STAT (PIAS)-derived SIM-containing peptides in a recent nuclear magnetic resonance study (Hecker *et al*, 2006). Basic residues required for transcriptional inhibition by SUMO2 are shown in red (Chupreta *et al*, 2005). Lysine (Lys; K) 37, Lys 39 and arginine (R) 54 in SUMO1 (circled) are proposed to have a role in electrostatic interactions with negatively charged residues in SIM-containing peptides (Baba *et al*, 2005; Hecker *et al*, 2006; Song *et al*, 2005). Lys 37 and Lys 39 in particular seem to interact with phosphorylated serine or threonine residues in SIMs. Not shown here is Lys 78, which might also have a role in SUMO1 SIM-binding (Hecker *et al*, 2006). SIMs, SUMO-interacting motifs; SUMO, small ubiquitin-like modifier.

the binding orientation. Various lysines of SUMO1 besides Lys 39 seem to have an important role in coordinating the phosphates and negatively charged amino acids of SIMs. One particular lysine, Lys 78 of SUMO1, is not conserved in SUMO2 and might therefore explain why SUMO2 interacts preferably with a SIM that lacks negatively charged residues (Hecker *et al*, 2006).

Preferences for SUMO1, -2 and -3. Crucial hydrophobic and basic residues that are involved in SIM binding are conserved among the SUMOs; however, the isoforms might differ in the placement of their hydrophobic groove. Crystallographic analyses show that the hydrophobic groove present in SUMO1, SUMO2 and yeast Smt3 is surrounded by basic residues, which reach up like prongs to accept the SIM domain and the associated negative charges (Chupreta *et al*, 2005). Intriguingly, the hydrophobic grooves in these isoforms occupy slightly different positions with respect to the basic residues, suggesting that the arrangement of hydrophobic and acidic residues in SIMs might dictate their ability to bind specific SUMO isoforms.

SUMO-interacting motifs compared with ubiquitin-binding domains. Only one SIM domain has been identified so far but there are at least 16 known ubiquitin-binding domains (UBDs; Hurley *et al*, 2006). Therefore, it would be surprising if a single SIM variant represents the only way in which proteins interact non-covalently with SUMO. Comparing SIMs with UBDs, SUMO and ubiquitin interact with opposite faces of the folded structure of these respective domains

Fig 2 | SUMO-interacting motif sequence, structure and SIM insertion between the $\beta 2$ strand and the $\alpha 1$ helix of SUMO. (A) Hydrophobic core amino acids of *bona fide* SIM domains in Srs2, thymine DNA glycosylase (TDG; Baba *et al*, 2005), DAXX (Lin *et al*, 2006) and promyelocytic leukaemia (PML; Shen *et al*, 2006) proteins discussed in this review. (B) Possible combinations of the hydrophobic (h) core of the SIM—often valines or isoleucines—in which X can be any amino acid. Blue spheres indicate acidic residues or phosphorylated serines or threonines. (C) Insertion of SIMs in one of two possible orientations depends on the arrangement of hydrophobic amino acids and negative charges juxtaposed to the hydrophobic groove of SUMO. Also shown here is a charged (red plus symbol) lysine (Lys 78) present in SUMO1 that might have an important role in orientating phosphorylated SIMs (Hecker *et al*, 2006). SIM, SUMO-interacting motif; SUMO, small ubiquitin-like modifier.

(Song *et al*, 2005). It has been suggested that the interactions between a UBD and ubiquitin almost always include the hydrophobic patch surrounding Ile44 on ubiquitin (Hicke *et al*, 2005); SUMO does not have a comparable Ile44 patch (Hicke *et al*, 2005; Hurley *et al*, 2006). In some cases, UBD-containing proteins can be prevented from interacting with ubiquitylated binding partners by mono-ubiquitylation in *cis* (Hoeller *et al*, 2006). It is unclear whether an analogous regulation exists for SIM-containing proteins (Fig 3C). Another obvious difference is that the affinities of SIMs for SUMO are in the 2–3 μ M range, whereas those of UBDs for ubiquitin have been described as weak, typically in the range of 10–500 μ M (Hecker *et al*, 2006; Hicke *et al*, 2005). This might indicate that, compared with ubiquitin–UBD interactions, SUMO–SIM binding relies to a lesser degree on multiple or tandem interactions. Tandem UBDs and multi-ubiquitylated proteins, among others, are believed to be the reason why UBDs and ubiquitin can generate physiologically relevant high-affinity interactions.

Functional implications of SUMO binding

The functional consequences of SUMO binding to SIM-containing proteins are beginning to emerge, and the number of biological pathways known to be regulated by non-covalent SUMO interactions is increasing. This section highlights a few tantalizing examples of SIM–SUMO interactions.

A potential role for SUMO-interacting motifs in DNA replication.

Once initiated, genome replication is committed to completion even when obstructions, such as DNA lesions and damaged replication forks, are encountered during DNA synthesis. Consequently, eukaryotic cells have an arsenal of proteins for DNA damage repair and bypass, including damage-tolerant DNA polymerases. These enzymes, in addition to other polymerases involved in regular replication, depend on the polymerase processing factor PCNA for their recruitment to the site of action. PCNA resides at replication forks and, depending on its post-translational modifications, provides a platform for the association of different polymerases and at least one DNA helicase, Srs2. Modifications of PCNA in budding yeast include mono- and poly-ubiquitylation as well as sumoylation (reviewed by Ulrich, 2005).

Sumoylation of PCNA was found to enhance error-free DNA replication in a process that is dependent on the Srs2 helicase. This is consistent with the finding that Srs2 interacts with both SUMO and PCNA (Hannich *et al*, 2005; Hoege *et al*, 2002; Papouli *et al*, 2005). Furthermore, the Srs2 helicase activity is also able to disrupt Rad51 nucleofilaments, a hallmark of homologous recombination (Krejci *et al*, 2003; Veaute *et al*, 2003). An elegant model consistent with these findings suggests that assembly of Rad51 nucleofilaments during replication is highly undesirable because it results in inappropriate homologous recombination that might stall and block replication fork progression, interferes with post-replicative repair and triggers prolonged cell-cycle arrest (Macris & Sung, 2005). Therefore, sumoylated PCNA might recruit the Srs2 helicase to prevent or disassemble the homologous recombination machinery at sites of DNA replication (Krejci *et al*, 2003; Papouli *et al*, 2005; Pfander *et al*, 2005; Veaute *et al*, 2003).

Consistent with the above hypothesis, the Srs2 protein is divided into distinct helicase, Rad51-binding and PCNA-interaction domains. The PCNA-interaction domain resides in the C-terminal tail of Srs2, and has been mapped to the last 138 residues of the protein (Pfander *et al*, 2005). SUMO modification of PCNA is not strictly required for its interaction with Srs2. A fragment of Srs2 encompassing the Rad51 and PCNA interaction domains (Srs2 Δ N) was able to interact with both sumoylated and non-sumoylated PCNA. However, free SUMO was able to compete with Srs2 Δ N for binding to sumoylated PCNA, suggesting a supporting role of SUMO in the interaction. Even more intriguingly, truncation of the six most C-terminal Srs2 Δ N amino acids (Glu-Ile-Ile-Val-Ile-Asp; EIIVID) resulted in a greatly reduced ability of this Srs2 fragment to interact with both SUMO and PCNA (Pfander *et al*, 2005). EIIVID fits the consensus V/I-X-V/I-V/I that allows SUMO to bind to SIMs, which suggests that at least one SIM might assist in the functional interaction between Srs2 and PCNA to prevent illegitimate recombination events during replication. If these data can be confirmed, particularly with a full-length Srs2 protein, the system should be suitable for a detailed mechanistic analysis of how enzymes that bind to SUMO assist PCNA to integrate signals and respond to conditions encountered at the replication fork. In this context, it

is unclear whether SIMs are also used to regulate the function of another helicase, Sgs1, which is involved in removing damaged replication forks (Branzei *et al*, 2006).

Controlled release and targeting of thymine DNA glycosylase. TDG prevents point mutations resulting from mismatched or altered bases. The enzyme removes mismatched thymine and uracil bases and creates abasic sites in double-stranded DNA. After binding and hydrolysis of a mismatched thymine, TDG remains tightly bound to the abasic site (Hardeland *et al*, 2002). The covalent modification of TDG with SUMO is the switch that releases TDG to allow the subsequent repair of the abasic site. Both the residues required for SUMO modification, as well as the residues in the SIM that mediate non-covalent binding, are necessary to release TDG from the DNA. Superimposition of TDG–SUMO onto a DNA substrate reveals a protruding helix in the protein structure that sterically interferes with DNA binding (Baba *et al*, 2005). The SIM and the lysine used for covalent modification of TDG are within a few amino acids of each other and might therefore both be required for this conformational change (Fig 3C). Indeed, the structure reveals a tight association of the covalently linked SUMO with the juxtaposed SIM. Therefore, binding of SUMO to the SIM of TDG might keep it correctly positioned for a conformational change and subsequent steric hindrance to occur. It should also be noted that the amino terminus of TDG is believed to form a reversible clamp for DNA binding, and that there is evidence that SUMO also interacts functionally with this clamp (Steinacher & Schar, 2005).

Finally, SUMO binding might also have a role in the localization of TDG. TDG localizes to promyelocytic leukaemia (PML) bodies and interacts with the PML protein. PML bodies, as described below, are sharply delineated nuclear subdomains associated with intense transcriptional activity and DNA repair. A TDG protein that lacks the SIM domain but still contains the SUMO consensus site for covalent modification is no longer covalently modified with SUMO. Furthermore, TDG lacking either the SIM or the SUMO consensus site still localizes to PML bodies; however, this localization is lost in the absence of both motifs (Takahashi *et al*, 2005). These findings suggest that before covalent modification, TDG binds SUMO through its SIM and that non-covalently and covalently associated SUMO have equivalent roles in PML targeting (compare Fig 3B–D).

SUMO-interacting motifs in promyelocytic leukaemia nuclear body assembly and function. When it comes to studying the functional interplay of SIMs with sumoylated proteins, nuclear PML bodies hold a wealth of examples. PML bodies are dynamic intranuclear structures that lack a membrane and are regulated in response to genomic stress and the cell cycle. The PML proteins act as the structural scaffold of these nuclear bodies, have crucial tumour-suppressive functions, and recruit a host of other proteins involved in transcription and the DNA-damage response (Borden, 2002). Among the resident proteins of PML bodies are the transcriptional repressor DAXX, the TDG protein and Ubc9, the SUMO E2-conjugating enzyme. A large proportion of PML and other proteins contained in these nuclear bodies are heavily sumoylated (reviewed by Seeler & Dejean, 2003). Furthermore, several of these proteins, such as PML, TDG, Ubc9 and SP100, interact non-covalently with SUMO (Hecker *et al*, 2006; Lin *et al*, 2006; Minty *et al*, 2000; Shen *et al*, 2006; Takahashi *et al*, 2005).

Fig 3 | SUMO-interacting motif-mediated opportunities for the regulation of protein sumoylation, conformation, localization and interaction.

(A–D) SUMO–SIM interactions in *cis*. (A) A protein (blue) might contain one or several SIM domains as well as SUMO (S) conjugation sites (lollipop shape labelled K). (B) SUMO binding to SIMs might precede, SUMO conjugation to the SUMO conjugation site (C; Takahashi *et al*, 2005). Recent data also suggest that conjugated SUMO can remain SIM-bound after conjugation and induce conformational changes in the substrate protein (C; Baba *et al*, 2005). (D) SUMO binding of *cis*-conjugated SUMO might be controlled (red X) by the accessibility of the SIM in *cis* (shown here) or in *trans*. (A,E,F) SUMO–SIM interactions in *trans*. (E) Recruitment of a SIM-containing protein to a sumoylated protein with a RING domain might precede sumoylation. This might be the case for the promyelocytic leukaemia (PML) protein (green; Shen *et al*, 2006). These interactions could be prevented by (C), the occupation of SIM domains by *cis*-conjugated SUMO, or the action of SUMO proteases of the ubiquitin-like protease (Ulp) family. (F) The ability of SUMO to form SIM-mediated higher-order protein complexes has earned it the reputation of ‘intra-molecular glue’ (Matunis *et al*, 2006). These protein complexes might recruit several types of sumoylated and SIM-containing proteins (light blue, yellow and green). The important role of SIMs in protein localization might contribute to the ability of individual proteins to find the correct multi-protein complex intracellularly, a process that is not well understood (Matunis *et al*, 2006). SIM, SUMO-interacting motif; SUMO, small ubiquitin-like modifier.

In vitro data suggest that PML itself might be sumoylated through the action of the E3 ligase RanBP2 (Tatham *et al*, 2005). However, the RING domain of PML—a hallmark of E3 ligases—might suffice to mediate its own sumoylation and possibly that of other proteins (Quimby *et al*, 2006; Shen *et al*, 2006). It has been suggested that the combination of SUMO and SIMs enables the interaction of many PML proteins to nucleate and establish a PML nuclear body scaffold (Shen *et al*, 2006). Sumoylated PML could also recruit a host of proteins through their SIMs, such as TDG, and might subsequently exert its SUMO ligase activity on them. In other words, SIMs might have a role in PML nuclear body formation, and mediate recruitment and SUMO modification of PML body resident proteins (Fig 3E,F).

DAXX regulation features some intriguing similarities to TDG. DAXX has at least eight different lysines that can be covalently sumoylated and also contains a SIM. When the entire SIM is deleted, DAXX fails to be covalently modified by SUMO, again suggesting that before covalent modification DAXX must be either correctly targeted through the SIM or that SUMO binding is a pre-requisite for the modification (Lin *et al*, 2006). SUMO1 mutants (Ile34 Glu, Val38 Lys or Lys45/46 Ala) that are defective in SIM interaction fail to be conjugated to DAXX, further suggesting that it is indeed SUMO binding that allows efficient sumoylation. As in the case of TDG, sumoylated PML uses the SIM of DAXX to recruit it to the nuclear body (Lin *et al*, 2006).

The functional relevance of the DAXX SIM seems to be in the tethering to and repression of promoter-binding complexes. Chromatin immunoprecipitation experiments have shown that DAXX, but not SIM-less DAXX, is part of the promoter-bound glucocorticoid receptor. The sumoylation state of DAXX in this complex does not seem to affect the repressive effect of DAXX, whereas the sumoylation state of the glucocorticoid receptor seems to have a role in transcription (Lin *et al*, 2006). This raises the important question of how many protein complexes, which depend on SIMs and SUMO, can co-exist in PML nuclear bodies and other parts of the cell, interact dynamically but not become intermingled (Matunis *et al*, 2006).

Potential SUMO-interacting motifs in SUMO-like domains: a role in the replicative stress response? Interestingly, certain proteins contain entire domains that are similar to ubiquitin or SUMO (Buchberger, 2002; Hartmann-Petersen & Gordon, 2004). Some proteins that contain SUMO-like domains have been implicated in transcriptional regulation and genome integrity (Novatchkova *et al*, 2005).

One protein containing SUMO-like domains is Rad60, a conserved protein that is important for the replication stress response (Boddy *et al*, 2003). The response to replication stress requires phosphorylation and self-association of Rad60. Curiously, this phosphorylation and self-association seem to depend, at least in part, on several potential SIMs in Rad60. The first potential SIM in the N terminus of Rad60 contains an SXS motif that becomes phosphorylated. Three additional potential SIM domains are found in the C terminus of Rad60 and reside within two SUMO-like domains (Raffa *et al*, 2006). Functionally, the N-terminal SXS motif is required for viability under conditions of replication stress. By contrast, the potential SIMs in the C-terminal SUMO-like domains are involved in Rad60 self-association. Despite the apparent functional importance of all potential SIMs in Rad60, little is known about how they interact with SUMO and with SUMO-like domains. Other studies, however, have revealed that SIMs within SUMO-like domains can interact non-covalently with SUMO (Rosendorff *et al*, 2004). At present, there are no structural insights into how SIMs in SUMO-like domains establish protein-protein interactions.

Conclusions

Studying the function that covalent SUMO modification imparts on a protein is often a thankless job. In only a few well-reviewed cases has mutating a SUMO consensus site of a SUMO substrate resulted in severe phenotypes that provide new insights into protein function. It seems possible that SIM-mediated SUMO binding can replace many of the functional aspects of covalent SUMO linkage to substrates (Takahashi *et al*, 2005). SIMs promote protein interactions, localize and target proteins, and might even be involved in changes in protein conformation and turnover (Minty

et al, 2000). With this insight comes a possible explanation for the observation that only a small fraction of a particular protein is sumoylated at any given time. For example, covalently SUMO-modified proteins might be found only where the recruitment of other SIM-containing proteins is required. This and many other questions about potential SIM functions remain unanswered, such as how accurate are the predictions of SIM-SUMO interaction and orientation that have been characterized in the most part for only very short peptides? Do some proteins with SIMs bind to SUMO chains? Could SIMs be used to recruit ubiquitin ligases to sumoylated proteins that are destined for proteasome-mediated degradation? What are the mechanisms that prevent proteins with SIMs from interacting with the wrong SUMO-modified protein? How many other motifs are there that can act as SUMO-interacting domains? However, one thing seems certain—interactions between SUMO and SIMs are already the basis for several new insights into SUMO biology; without a doubt there are more to come.

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