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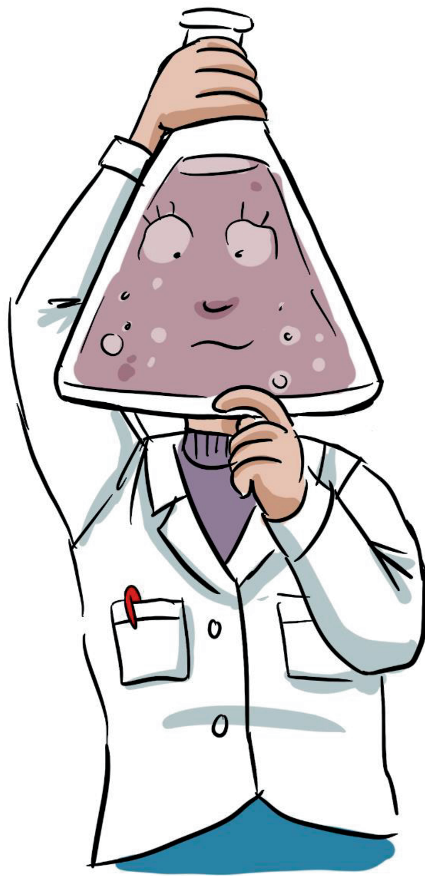

Chapter 2

A Chain of Events: Regulating Target Proteins by SUMO Polymers

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Abstract

Small ubiquitin-like modifiers (SUMOs) regulate virtually all nuclear processes. The fate of the target protein is determined by the architecture of the attached SUMO protein, which can be of polymeric nature. Here, we highlight the multifunctional aspects of dynamic signal transduction by SUMO polymers. The SUMO-targeted ubiquitin ligases (STUbLs) RING-finger protein 4 (RNF4) and RNF111 recognize SUMO polymers in a chain-architecture-dependent manner, leading to the formation of hybrid chains, which could enable proteasomal destruction of proteins. Recent publications have highlighted essential roles for SUMO chain disassembly by the mammalian SUMO proteases SENP6 and SENP7 and the yeast SUMO protease Ulp2. SENP6 is particularly important for centromere assembly. These recent findings demonstrate the diversity of SUMO polymer signal transduction for proteolytic and nonproteolytic purposes.

Ubiquitin and Ubiquitin-Like Modifiers

Several processes can modulate proteins beyond their composition predetermined at the DNA level, including protein processing and post-translational modifications (PTMs). Ubiquitylation and SUMOylation are PTMs that are similar concerning the enzymatic cascades they use for conjugation and deconjugation, and despite their limited sequence identity of only 18% [1], they are comparable regarding their 3D structure, known as the β-grasp fold [2]. The conjugation of both molecules involves three steps performed by three classes of enzymes known as the E1 activating enzyme, the E2 conjugating enzyme, and the E3 protein ligase. The functional outcome of the modification depends on its nature, being monomeric, multimonomeric, or polymeric, with possibly branched chains (Figure 1) [3]. Ubiquitylation and SUMOylation are not mutually exclusive on protein substrates and can coexist on targets via different acceptor lysines or via mixed chains, functioning as modified modifiers [4, 5].

Although the structure and conjugation pathways of ubiquitin and SUMO are similar, their functions are unique since they cannot compensate for each other. Target substrates conjugated with monoubiquitin have been linked to trafficking, protein sorting, and chromatin regulation, while substrates conjugated to most forms of polyubiquitin are targeted for degradation by a multisubunit ATP-dependent protease complex known as the 26S proteasome or via ubiquitin-dependent autophagy, regulating a broad variety of cellular processes such as cell cycle progression and genome stability [6, 7, 8]. Distinct types of ubiquitin chain architecture can have different functions, including the degradation-independent roles of K63-linked ubiquitin chains [9, 10].

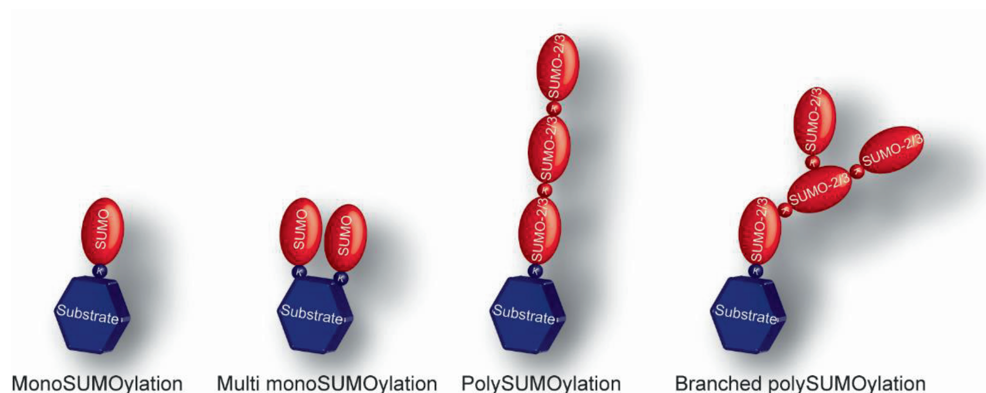

Figure 1. Conjugation of Small Ubiquitin-Like Modifiers (SUMOs) on Substrates.
Differential architecture of SUMO molecules attached to lysine residues on target proteins. SUMO can be attached to the target protein by monoSUMOylation, multiSUMOylation, or polySUMOylation.

SUMO is not generally associated with protein degradation but is implicated in protein–protein interactions, protein activity, and protein subcellular localization. Cellular processes dependent on SUMOylation are transcription, pre-mRNA splicing, ribosome maturation, cell growth, cell division, and the maintenance of genome stability [11, 12, 13, 14, 15]. PolySUMOylation of target substrates has been observed in response to replication arrest and various forms of cellular stress, including heat shock [16, 17, 18, 19]. However, compared with our extensive knowledge on ubiquitin polymers, we are still limited in our understanding of signaling by SUMO polymers. The ability of SUMO to form polymers is the main focus of this review. Here we elaborate on the SUMO family members that are able to form polymers and on STUbLs. Moreover, specific proteases that are able to cleave SUMO polymers are discussed, including the mammalian proteases SENP6 and SENP7 and the yeast Ulp2. These proteases are essential for numerous processes such as genome stability, cell cycle progression, and the DNA damage response [15, 20]. Furthermore, polymeric SUMO signaling in meiosis, in mouse embryonic development, and in yeast is discussed.

SUMO Family Members SUMO-2 and SUMO-3 Form Ubiquitin-Like Polymers on Target Proteins

Mammals express at least three SUMO family members. The functional outcome of protein modification by SUMO is dependent on the identity of the SUMO family member conjugated to the target protein. Mature SUMO-2 and SUMO-3 are nearly identical, sharing 97% sequence identity, and are collectively named SUMO-2/3. Mature SUMO-2/3 share a 47% overlap with mature SUMO-1. The concentration of free SUMO-2/3 in cells is higher than that of free SUMO-1 [21]. Some target proteins are preferentially conjugated to SUMO-2/3 or SUMO-1 and other targets can be conjugated by either [22]. Interestingly, SUMO-2/3 are able to form ubiquitin-like polymers on target proteins [23]. MonoSUMOylation and polySUMOylation should be regarded as different signals.

Assembly Mechanism of Polymeric SUMO Chains and Disassembly by Dedicated SUMO Proteases

SUMO-2/3 chains form preferably on lysine residue 11 situated in a SUMO consensus site, ψKxE (ψ is a large hydrophobic amino acid such as I, V, or L), although alternatively linked, noncanonical chains also exist [24]. SUMO-1 contains an inverted SUMO consensus site, ExK [25]. SUMO consensus sites are recognized by the SUMO E2 enzyme Ubc9, thereby promoting the formation of chains [26, 27, 28].

E3 ligases enhance the transfer of SUMO proteins from E2 to substrates [11, 29]. E3 ligases can have E4 elongase activity to extend and promote the formation of SUMO chains on target substrates [30,31]. Until now, a limited set of these ligases has been described. One type of E3 ligase is the protein inhibitor of activated STAT (PIAS) family, which comprises PIAS1–4. Members of this family contain the SP-RING domain, a conserved RING-finger-like domain, similar to ubiquitin E3 ligases, which enables binding to Ubc9 [32]. PIAS family members have been initially described to act as transcriptional co-regulators [33], but recent findings have also shown the importance of PIAS members in signal transduction pathways regulating protein stability, cellular proliferation, and DNA repair by interacting with up to 60 cellular partners [34, 35, 36]. A more recently identified SUMO E3 ligase with E4 elongase activity is zinc-finger protein 451 (ZNF451), which has a preference for SUMO-2/3 [30]. It contains an N-terminal tandem-SUMO interaction motif (SIM) region, which is sufficient to anchor the SUMO molecule and initiate chain formation by its zinc-finger region [29]. ZNF451 plays a role in response to stress and transcription by regulating the SUMOylation of the promyelocytic leukemia gene product PML and by interacting with Smad3/4, which ultimately leads to the inhibition of the TGF-β pathway [37, 38, 39]. These E3 ligases provide substrate specificity and aid in the formation of SUMO-2/3 chains, which can act as recruitment signals for other PTM enzymes as described in the next section.

Attachment to target proteins can be reversed by a family of cysteine proteases called SENPs. The human genome encodes six members of the SENP family: SENP1, SENP2, SENP3, SENP5, SENP6, and SENP7, each having their own function and subcellular localization [40]. SENPs enable the maturation of SUMO precursors by proteolytic cleavage of their carboxyl termini, exposing a diglycine motif essential for conjugation. Furthermore, SENPs act as deconjugating enzymes to remove SUMO from substrates, and depolymerize polySUMO-2/3 chains. SENP1 has a preference for SUMO-1, whereas the other SENP family members have a preference for SUMO-2/3 [40, 41]. SENP6 and SENP7 differ from other SENP family members due to an insertion in their conserved catalytic domains that enables their preference for SUMO-2/3 chains [42].

Regulation of SUMO Polymers by STUbLs in a Chain-Architecture-Dependent Manner

Since the discovery of SIM-containing ubiquitin E3 ligases, known as STUbLs, considerable effort has been made to reveal their function and their regulatory effects on SUMO chains [43]. STUbL-mediated ubiquitylation regulates SUMOylation homeostasis by promoting target protein degradation or by altering the subcellular localization of proteins, establishing crosstalk between SUMOylation and ubiquitylation [4 ,44, 45]. SUMO chain formation acts as a recruitment signal for STUbLs since they enable preferential binding to tandem SIMs (Figure 2) [46, 47, 48]. Whether the reverse scenario, ubiquitin-targeted SUMO ligases, exists is currently unclear.

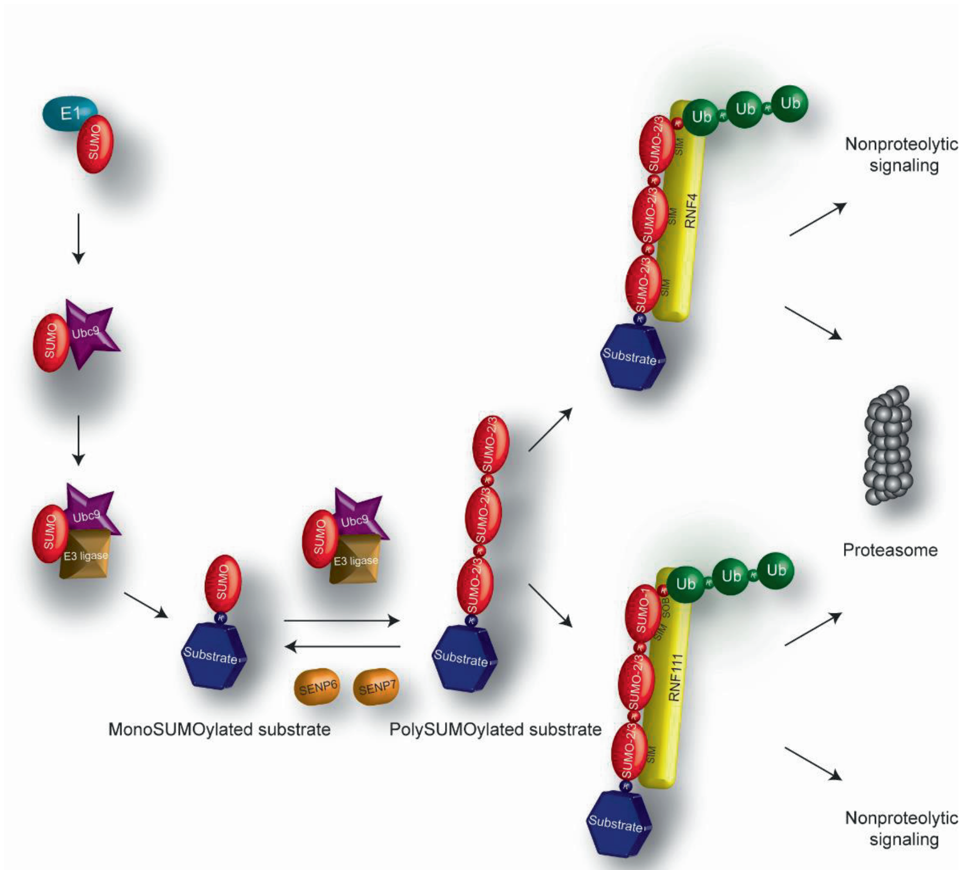

Figure 2. Formation of Poly-Small Ubiquitin-Like Modifier (SUMO)-Ubiquitin Hybrid Chains. Mature SUMO proteins are activated by attachment via a thioester bond to a heterodimeric E1 SUMO-activating enzyme. Subsequently, activated SUMOs are transferred to the catalytic cysteine residue of the E2 conjugating enzyme (Ubc9; novel nomenclature UBE2I). Thereafter, SUMOs are attached to lysine residues of the target protein, which is facilitated by E3 SUMO ligases. SUMO proteins can be detached from target proteins by specific proteases. MonoSUMOylation can be reversed by the SUMO proteases SENP1–3 and SENP5. Substrates can also be polySUMOylated with the help of E3 ligases containing E4 elongase activity. These polySUMO chains can be cleaved by SENP6 and SENP7. Furthermore, SUMO-targeted ubiquitin ligases (STUbLs) can recognize SUMO polymers via multiple SUMO interaction motifs (SIMs). SIMs comprise a string of large hydrophobic residues that can be flanked by acidic residues. STUbLs can conjugate ubiquitin to SUMO polymers to form hybrid chains. These hybrid chains can act as targeting signals for degradation by the 26S proteasome. RING-finger protein 111 (RNF111) has a preference for SUMO chains capped with SUMO-1, having the ability to ubiquitylate and form hybrid chains, either targeting substrates for proteasomal degradation or mediating signaling in a nonproteolytic manner.

Following the identification of a STUbL in yeast, the first STUbL found in mammals was RNF4 (also known as SNURF), containing four N-terminal SIMs and a C-terminal RING-finger domain. Mechanistically, RNF4 maintains SUMO signaling homeostasis by directly controlling the auto-SUMOylated E2 conjugating enzyme Ubc9 and auto-SUMOylated E3 ligases (Figure 3) [49]. Arsenic-induced polySUMOylation of PML and PML-RARα acts as a recruitment signal for RNF4 enabling subsequent K48-linked polyubiquitylation, leading to proteasomal degradation [50, 51]. Interestingly, ZNF451-1, a SUMO E3 ligase, and RNF4 appear to cooperate in maintaining PML levels by acting on the same target protein [39] whereas RNF168, another ubiquitin E3 ligase, might act downstream of RNF4 by regulating PML-NBs by the efficient binding of K63-linked hybrid chains [52]. RNF4 is important to maintain genome stability, by regulating DNA damage response components such as MDC1, BRCA1, PARP1, and JARID1B/KDM5B [53, 54, 55, 56]. However, the regulatory function of RNF4 goes beyond merely tagging cellular proteins for ubiquitin-mediated degradation. Modifications by RNF4 can alter the subcellular localization and functional dynamics of target substrates [57]. As an example, RAP80, the first characterized SUMO-ubiquitin chain receptor, recognizes K63-linked ubiquitin chains formed by RNF4 and can hereby mediate BRCA1 recruitment to DNA damage sites [58].

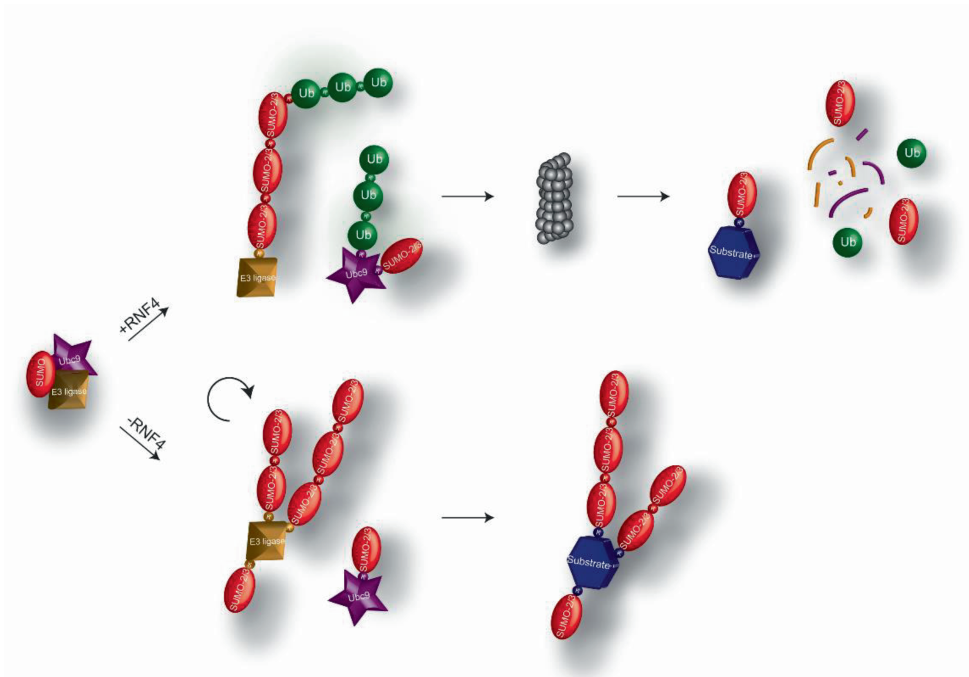

Figure 3. RING-Finger Protein 4 (RNF4) Acts as a Brake on Small Ubiquitin-Like Modifier (SUMO) Signal Transduction. AutoSUMOylated E2 and E3 enzymes including PIAS1, PIAS2, PIAS3, ZNF451, and NSMCE2 are preferentially ubiquitylated by RNF4 and subsequently targeted to the proteasome, thereby limiting SUMO signal transduction. In the absence of RNF4, autoSUMOylated active E2 and E3 enzymes continue to SUMOylate substrates, leading to increased SUMOylation levels in cells.

A second STUbL is Arkadia (RNF111) [59]. Arkadia is able to noncovalently attach to SUMO-2/3 polymers as expected for a STUbL, enabled by its three SIM motifs [60]. Depletion of this STUbL leads to polySUMOylated PML accumulation, suggesting that Arkadia and RNF4 both regulate polySUMO-PML degradation. However, Arkadia does not heterodimerize with RNF4, indicating that these two STUbLs interact independently in the process of PML degradation [61]. Interestingly, RNF4 has a preference for homogenous SUMO-2 chains while Arkadia employs two SIMs (type r and type b SIMs) and a SUMO-1-binding motif (SOB) to preferentially bind to SUMO-2 chains capped with SUMO-1, with a higher targeting efficiency for three SUMO-2 moieties or more [62]. Moreover, Arkadia targets the SMAD inhibitor SMAD7, thereby promoting the TGF-β and bone morphogenetic protein (BMP) signaling pathway [63, 64]. Whether this involves SUMOylation of SMAD7 is currently unclear. However, Arkadia also has a nonproteolytic function by modifying SUMOylated targets such as xeroderma pigmentosum C (XPC) with

a K63-linked ubiquitin chain in response to UV-induced DNA damage [60] or with a K48-linked ubiquitin chain as is the case for the polySUMOylated transcription factor Nrf2, surprisingly enabling its stabilization [65]. The investigation of STUbLs is important to understand the functionality of SUMO polymers and SUMO-ubiquitin hybrid chains.

Depolymerization of SUMO Chains Is Vital for Genome Stability and Accurate Mitosis and Is Required for Assembly of the Constitutive Centromere-Associated Network (CCAN)

As mentioned earlier, SENP6 and SENP7 are inefficient in processing SUMO precursors and in removing monoSUMO from substrates, but they are particularly efficient in depolymerizing SUMO-2/3 chains [66, 67]. Both SENP6 and SENP7 contain several SIM domains, which might enable preferential recognition of SUMO chains [68, 69]. SENP6 is highly efficient in processing SUMO chains and the depletion of either SENP6 or SENP7 leads to the accumulation of high-molecular-mass polySUMO-2/3 conjugates in PML subnuclear bodies [66, 70, 71].

Cells depleted of SENP6 are severely compromised in proliferation and accumulate polySUMO chains on over 200 proteins [15]. These targets include most kinetochore components that belong to the CCAN. The CCAN facilitates the physical attachment of centromeres to spindles formed by microtubule polymers [72]. Removal of SUMO from CCAN members is important for their accumulation at centromeres to enable accurate chromosome segregation, leading to correct progression of the cell cycle (Figure 4). Cellular defects include improper spindle assembly, reduced metaphase chromosome congression, and the formation of micronuclei due to the reduction of most CCAN members at the kinetochore [15, 72, 73]. This points to functional protein group demodification, demonstrating the cooperative regulation of a functional group of proteins by SENP6. This is consistent with earlier observations that SUMOylation acts via functional protein group coregulation [74, 75]. The reduced accumulation of CCAN members at the kinetochore is possibly due to steric hindrance by SUMO chains as an underlying mechanism [15] and not due to RNF4-mediated proteasomal degradation as proposed earlier [72]. In yeast, Ulp2 is present at centromeres to enable SUMO removal from CCAN members [20]. By contrast, in mammalian cells SENP6 does not accumulate at centromeres but is thought to remove SUMO chains from centromeric proteins in the nucleoplasm to enable their subsequent accumulation at centromeres [15]. Interestingly, SENP6 also has a critical role in DNA replication and in the DNA damage response [15]. SENP6 deSUMOylates RPA70 (RPA1) that is part of the replication protein A (RPA) complex, leaving it in a hypoSUMOylated state during S phase [68, 76]. However, RPA70 was not identified in our unbiased screen for SENP6 target proteins [15]. The central components of the Fanconi anemia (FA) DNA repair pathway, FANCI and FANCD2, are

SUMOylated with the help of SUMO E3 ligases PIAS1/PIAS4 during replication stress, enabling subsequent ubiquitylation by RNF4 and extraction by the DVC1-p97 complex. SENP6 antagonizes this pathway, showing a versatile role in the DNA damage response [77].

Moreover, SUMO chains are assembled on proteins at double-stranded DNA breaks in response to DNA-damaging agents and their deconjugation by SENP7 plays an important role in chromatin relaxation and DNA repair by homologous recombination. SENP7 does this, for example, by removing SUMO-2/3 polymers from KRAB-associated protein1 (KAP1/TRIM28) and by regulating CHD3 at the chromatin, thereby promoting DNA repair mechanisms [69]. SENP7 also has a regulatory effect in innate immunity by removing SUMO as a cGAS-STRING inhibitor, thereby fine-tuning immune and inflammatory responses [78]. Taking these findings together, the removal of polySUMO from substrates by SENP6 and SENP7 is important for multiple cellular processes related to oncogenesis. Therefore, SENP6 and SENP7 might act as valuable targets for drug development in the fight against cancer.

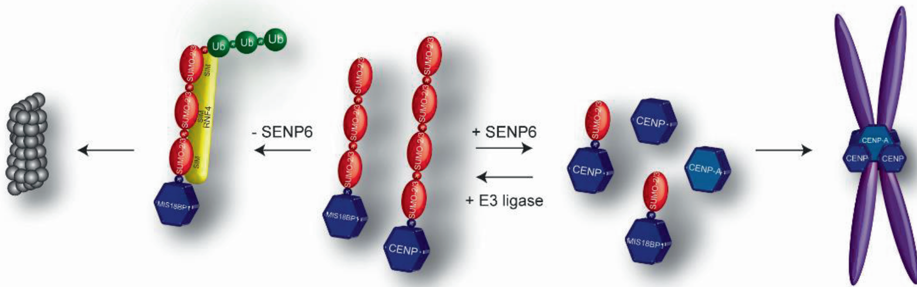

Figure 4. Protein Group deSUMOylation by SENP6. Depicted are the SENP6-regulated proteins Mis18BP1 and members of the constitutive centromere-associated network (CCAN). In the presence of SENP6, poly-small ubiquitin-like modifier (SUMO) chains are removed and CENP proteins localize to the kinetochore where Mis18BP1 is important for CENP-A loading. However, in the absence of SENP6, polySUMOylated Mis8BP1 is ubiquitylated by the SUMO-targeted ubiquitin ligase (STUbL) RING-finger protein 4 (RNF4) and subsequently targeted to the proteasome for degradation, while polySUMOylated CCAN members fail to properly accumulate at centromeres, possibly due to steric hindrance.

SUMO Polymers Are Vital in Meiosis

Meiosis is a specialized division in which DNA replication, synapsis, and segregation steps produce haploid gametes. Meiotic spindles lack centrosomes, in contrast to mitotic spindles, and follow a different, two-step segregation pathway (meiosis I and meiosis II). Errors in this process can lead to aneuploidy, eventually causing infertility and birth defects in mammals. An interplay between SUMO and ubiquitin during meiotic recombination in mice has been suggested, whereby the presumed SUMO E3-ligase RNF212 stabilizes factors at recombination sites [79]. However, *in vitro* biochemical evidence for a role of RNF212 as a SUMO E3 ligase is currently not available. A potential STUbL, HEI10, might interact with RNF212 along chromosome axes, thereby regulating the SUMO and ubiquitin-proteasome system and influencing events of meiotic prophase in the mouse [80]. In *Caenorhabditis elegans*, a multiprotein ring complex (RC) situated between chromosomes is important for oocyte meiosis. Several components of the RC, such as the kinase BUB-1 and the SUMO E3 ligase GEI-17/PIAS, contain SIMs and can be SUMOylated, leading to the recruitment of SUMO target proteins into the RC, which are needed for correct chromosome congression [81]. Thus, a delicate balance between SUMO conjugation and deconjugation regulates the stability of the RC. Smt3 deconjugation in yeast by the protease Ulp1 is important for RC disassembly and completion of the meiotic divisions [82]. Interestingly, transcription of Ulp2, responsible for Smt3 polymer modification, increases at the early meiotic stage and poly-Smt3 protein conjugates change throughout meiosis [83]. This shows the importance of SUMO in meiotic events and highlights the dynamic nature of SUMO polymer conjugation to and deconjugation from target proteins, which is important for correct chromosome segregation across species.

SUMO Polymers in Mice

In vivo mouse experiments have shown the importance of several components of the SUMO pathway for viability during embryogenesis [84]. Interestingly, SUMO-1 is not necessary for embryonic development, since its loss can be compensated for by SUMO-2/3, whereas SUMO-2 is the most abundant and therefore the essential SUMO family member [85, 86]. Cleavage of SUMO polymers is of importance, as *in vivo* knockdown of SENP6 causes upregulation of proinflammatory cytokines by potentiating NFκB-responsive genes, thereby increasing the death rate of mice by endotoxic shock [87]. SENP6 regulates osteochondroprogenitors (OCPs) during skeletal development by maintaining TRIM28 levels, consequently regulating p53 activity [88]. The SUMO protease SENP7 is also important in mice to maintain HP1α accumulation at pericentric heterochromatin and to regulate DNA repair by interacting with the chromatin remodeler CHD3 [69, 89]. Mouse SENP7-deficient oocytes arrest in meiotic prophase I and metaphase I while SENP7-deficient embryos display decreased blastocyst production and induced embryonic death

due to hampered zygotic DNA repair [90]. Taken together, *in vivo* knockout/down experiments have shown an indispensable role for SUMO chain depolymerization in mouse embryonic development.

SUMO Polymers in Yeast

The single cellular organisms *Saccharomyces cerevisiae* and *Schizosaccharomyces pombe* are able to form SUMO chains via the presence of internal acceptor lysine residues [16, 91], showing that the occurrence of SUMO polymers is not limited to vertebrates. In yeast, the DNA helicase Sgs1, forming a complex with Top3 and Rmi1, has a preference for polySUMO chains and associates with the SUMO E3 Smc5/6 to remove DNA recombination intermediates important in genome stability [92]. Moreover, the Mre11-Rad50-Xrs2 (MRX) complex catalyzes double-stranded break repair, whereby Mre11 noncovalently binds to polySUMO moieties through its SIM, thereby promoting the SUMOylation of DNA repair proteins [93]. The formation of hybrid ubiquitin-SUMO chains also occurs in yeast [94], facilitated by STUbLs known as synthetic lethal of unknown function 5 (Slx5), Slx8, Rfp1 (RNF1), Rfp2, and Uls1. These STUbLs are able to heterodimerize via their RING domains, forming the functional E3 ligases Slx5/8 and Rfp1/2 [44, 95]. DeSUMOylation is required for growth and to cope with replication stress [96]. While Ulp1 is thought to deSUMOylate an extensive number of substrates, Ulp2 is thought to be more substrate specific and is recruited to transcriptionally active genes [97,98]. Knockout of Ulp2 leads to the accumulation of specific Smt3–protein conjugates and subsequent loss of chromosomes, abnormal mitotic spindles, poor recovery from cell cycle check point arrest, and inefficient replication onset [83, 99, 100, 101]. Consequently, yeast deficient for Ulp2 display aneuploidy and an increase in transcription levels across two chromosomes leading to an increase of two genes, *CLN3* and *CCR4*, to counteract the loss of this essential protease [102, 103]. It has been proposed that Ulp2 recognizes a minimum of three SUMO moieties and trims SUMO polymers from the distal end [104]. Overexpression of Ulp2 leads to suppression of the *MIF2* gene, a homolog of the mammalian centromere protein CENP-C [105]. Impaired recruitment of Ulp2 and/or its perturbed binding to SUMO results in an increased rate of chromosome loss, hypersensitivity to DNA replication stress, and elevated levels of SUMOylation on CCAN members, indicating a dual substrate recognition mechanism via a kinetochore-targeting motif [20]. Ulp2 prefers polySUMOylated substrates through its C-terminal regulatory domain, containing three conserved motifs including a SIM domain, targeting its SUMO protease activity to Smt3 polymers [106]. The Smt3 protein is an essential gene; however, chain formation is not a prerequisite for viability in *S. cerevisiae* [99]. The data indicate that SUMO chain formation could be dispensable for some organisms, whereas SUMO chain disassembly is essential.

Concluding Remarks

Since the SUMO protein was discovered, a considerable amount of genetic and proteomic research has been performed in the quest to unravel its function. Over the years it has become clear that not only monoSUMOylation is an important regulatory cue but also polySUMOylation, which acts as, for example, a recruitment signal for STUbLs. It has been observed that the polymeric form of SUMO plays an important role in a broad range of cellular mechanisms, varying from the regulation of subcellular localization to influencing DNA repair mechanisms. Deregulation of these processes can lead to the onset of diseases. A role for polymeric SUMOylation has been described in Alzheimer's disease, influencing amyloid-β peptide generation whereby polySUMO reduced Aβ regeneration [107], and might be involved in Gordon Holmes syndrome whereby the ubiquitin ligase RNF216 recognizes SUMO-2 chains in a nonproteolytic manner [108]. Moreover, a role for polySUMO-2/3 and RNF4 has been described in the degradation of misfolded ataxin-7 (polyQ-ATXN7), a hallmark of the neurodegenerative disease spinocerebellar ataxia type 7 (SCA7) [109]. In addition, RNF4 regulates the compartmentalization of an amyotrophic lateral sclerosis (ALS)-associated FUS mutant in stress granules [110]. Polymeric SUMOylation has also been associated with cancer, affecting various proteins important for, for example, the DNA damage response, cell cycle progression, and correct chromosome segregation [15, 48, 76, 111]. It is important to obtain a full view of the complete SUMO pathway and its functional effects on target substrates. Cutting-edge proteomic screens can now be performed using mass spectrometry and data mining, which might contribute to the discovery of new target proteins. Novel STUbLs might be found in the large pool of ubiquitin ligases, revealing more crosstalk between these two modifiers, which could be of use in the search for therapeutic agents to block tumor cell proliferation. Increased target SUMOylation has been associated with poor disease outcomes, and therefore inhibiting the SUMO machinery could be a solution [112, 113]. ML-792 is a potent SUMOylation inhibitor, targeting the SUMO E1 enzyme [114]. Blocking this enzyme, which could potentiate several oncogenes such as c-Myc and FoxM1 and might contribute to cancer progression, has shown to be promising in preclinical models of colorectal cancer [115, 116]. In addition to targeting the SUMO conjugation system, it could also be useful to target the SUMO deconjugation machinery as a potential anticancer therapy since depletion of SENP6 leads to several mitotic defects, ultimately causing cells to stop their proliferation. This implies that inhibitors of SENP6 and possibly SENP7 could also be considered in the fight against cancer.

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