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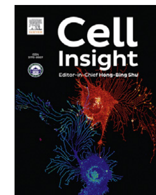
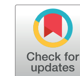


The role of SUMOylation in biomolecular condensate dynamics and protein localization



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A B S T R A C T

As a type of protein post-translational modification, SUMOylation is the process that attaches a small ubiquitin-like modifier (SUMO) to lysine residues of protein substrates. Not only do SUMO and ubiquitin exhibit structure similarity, but the enzymatic cascades for SUMOylation and ubiquitination are also similar. It is well established that protein ubiquitination triggers proteasomal degradation, but the function of SUMOylation remains poorly understood compared to ubiquitination. Recent studies reveal the role of SUMOylation in regulating protein localization, stability, and interaction networks. SUMO can be covalently attached to substrates either as an individual monomer (monoSUMOylation) or as a polymeric SUMO chain (polySUMOylation). Strikingly, mono- and polySUMOylation likely play distinct roles in protein subcellular localization and the assembly/disassembly of biomolecular condensates, which are membraneless cellular compartments with concentrated biomolecules. In this review, we summarize the recent advances in the understanding of the function and regulation of SUMOylation, which could reveal potential therapeutic targets in disease pathogenesis.

1. The SUMOylation pathway

1.1. SUMO and ubiquitin

Although considered a member of the ubiquitin-like protein family, a small ubiquitin-like modifier (SUMO) possesses distinct features that set it apart from ubiquitin (see Table 1 for all abbreviations). The SUMO gene (*SMT3*) was first identified in budding yeast *Saccharomyces cerevisiae* by Meluh and Koshland during a genetic screen for suppressors of a kinetochore protein mutant, *mif2* (Meluh & Koshland, 1995). SUMO shares 18% sequence similarity with ubiquitin, and structural studies have shown that both contain a "ββαββαβ" ubiquitin fold, known as the β-grasp fold, and a diglycine motif at their C-terminus (Bayer et al., 1998). This conserved motif is critical for isopeptide bond formation during protein modification. In contrast to ubiquitin, all SUMO proteins are characterized by an intrinsically disordered N-terminus comprised of 13–23 amino acids (Bayer et al., 1998). The intrinsically disordered region (IDR) is crucial for native protein conformation, as N-terminal deletion mutants cause deleterious SUMO aggregation (Sabate et al., 2012). So far, five isoforms of SUMO (SUMO1-5) have been identified in mammalian cells (Acuña et al., 2023), but budding yeast has a single SUMO, Smt3.

1.2. The SUMOylation conjugation enzymatic cascade

SUMOylation is a reversible, covalent post-translational modification that involves the attachment of SUMO to targeted proteins. Although the SUMO gene was first identified in budding yeast, studies in human cells were the first to demonstrate SUMOylation of proteins. These substrates include DNA damage repair proteins RAD51 and RAD52, cell surface death receptor FAS, and promyelocytic leukemia (PML) protein (Boddy et al., 1996; Okura et al., 1996; Shen et al., 1996). Interestingly, SUMOylation is catalyzed by a cascade of enzymes similar to ubiquitination. Like ubiquitination, the SUMO conjugation pathway involves several enzymatic steps: activation, conjugation, and ligation (Fig. 1). However, unlike ubiquitination, newly synthesized SUMO requires cleavage at the C-terminus by specific SUMO proteases for maturation (Nayak & Müller, 2014), which exposes a diglycine motif essential for adenylation. The activation of matured SUMO is ATP-dependent and catalyzed by E1 heterodimer Aos1-Uba2 in budding yeast, where ATP is used to form a SUMO-adenylate conjugate intermediate (Johnson et al., 1997). Once the SUMO-adenylate conjugate forms through a thioester bond, SUMO is transferred to Ubc9, the E2 conjugating enzyme (Johnson & Blobel, 1997). Finally, SUMO is transferred to a target protein, forming a covalent bond with a lysine residue within a SUMO consensus motif

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Table 1
Abbreviations used in this review.

Abbreviation	Full Name
SUMO	Small ubiquitin-like modifier
IDR	Intrinsically disordered region
PML	Promyelocytic leukemia
SIM	SUMO interacting motif
LLPS	Liquid-liquid phase separation
RENT	Regulator of nucleolar silencing and telophase
CPC	Chromosomal passenger complex
MCM	Minichromosome maintenance complex
STUbL	SUMO-targeted ubiquitin ligase
TMM	Telomere maintenance mechanism
ALT	Alternative lengthening of telomeres
APB	ALT-associated PML bodies
DDR	DNA damage response

(ψKX(D/E)), where ψ is a large hydrophobic residue, and X is any residue (Mahajan et al., 1998; Matunis et al., 1998). E3 SUMO ligases mediate the transfer of SUMO from Ubc9 to a target protein (Johnson & Gupta, 2001). Compared to the wide array of E2 and E3 enzymes in the ubiquitin conjugation pathway, SUMOylation relies on a single E2 enzyme (Ubc9) to mediate the conjugation of SUMO. In addition, far fewer E3 enzymes for SUMOylation have been identified in comparison to ubiquitination. Despite the fewer number of SUMO enzymes, thousands of SUMO targets have been identified, indicating less substrate specificity for SUMOylation. Therefore, group SUMOylation, or the SUMOylation of multiple targets within a complex, may contribute to the modification of a large number of substrates (Hendriks & Vertegaal, 2016; Lamoliatte et al., 2017; Li et al., 2020).

SUMO conjugation can be monomeric, multi-monomeric, or polymeric. The presence of SUMO proteases can reverse SUMOylation (Kunz et al., 2018). In mammalian cells, SUMO-2 and SUMO-3 are involved in protein polySUMOylation, whereas SUMO-1 is responsible for monoSUMOylation and functions as a terminator of polySUMO chains (Tatham et al., 2001). The family of sentrin/SUMO-specific proteases in mammalian cells includes SENP1, SENP2, SENP3, SENP5, SENP6, and SENP7, which share 20–60% catalytic domain sequence identity (Mukhopadhyay & Dasso, 2007). Among them, SENP6 and SENP7 prefer deconjugating SUMO-2/3 polySUMO chains. Budding yeast contains two SUMO proteases, Ulp1 and Ulp2/Smt4 (Li & Hochstrasser, 1999; Strunnikov et al., 2001). SENP1-3 and SENP5 in mammalian cells are evolutionarily related to Ulp1, while SENP6 and SENP7 show higher sequence identity to Ulp2 (Nayak & Müller, 2014). In budding yeast, Ulp1 is essential for viability, because it not only deSUMOylates cytoplasmic proteins but also cleaves Smt3 for maturation (Li & Hochstrasser, 2003). Ulp2 is nonessential and acts predominantly on nuclear proteins. In addition, Ulp2 specifically associates with polySUMO chains (Liang et al., 2017), processing substrate-linked polySUMO chains from their distal ends down to two linked SUMO moieties (Eckhoff & Dohmen, 2015; Li & Hochstrasser, 1999, 2000; Strunnikov et al., 2001). Therefore, budding yeast Ulp2 and human SENP6-7 are the key SUMO proteases in preventing polySUMOylation of nuclear proteins.

1.3. The interaction between SUMO and SUMO-interacting motifs (SIMs) facilitates assembly of biomolecular condensates

In addition to the covalent attachment of SUMO to lysine, a wide array of substrates bind to SUMO or SUMO chains through non-covalent interactions. These SUMO-interacting motifs (SIMs) are characterized by a hydrophobic core flanked by acidic or phosphorylatable serine residues (Hecker et al., 2006). SUMO-SIM interactions can lead to the formation of large protein complexes and facilitate the nucleation of liquid-liquid phase separation (LLPS) (Banani et al., 2016). LLPS has emerged as a central mechanism in the assembly of membraneless compartments known as biomolecular condensates (Laflamme & Mekhail, 2020). Furthermore, previous studies have highlighted the critical role of IDRs within SUMO in condensate formation (Brangwynne et al., 2015; Zhou et al., 2018). Because the IDR domain lacks a fixed three-dimensional structure, it can achieve high conformational flexibility and is able to modulate the protein network in phase separation (Majumdar et al., 2019).

The formation of biomolecular condensates in cells has been readily observed in a variety of contexts, including nuclear domains known as promyelocytic leukemia (PML) nuclear bodies (PML condensates). These condensates were first recognized in acute promyelocytic leukemia (APL). PML condensates are well-known as centers for nuclear protein quality control, although their complete biological function is not fully understood (Gärtner & Muller, 2014; Guo et al., 2014; Keiten-Schmitz et al., 2021). The formation of PML condensates begins with PML itself, as SUMOylated PML serves as a scaffold protein for condensate assembly

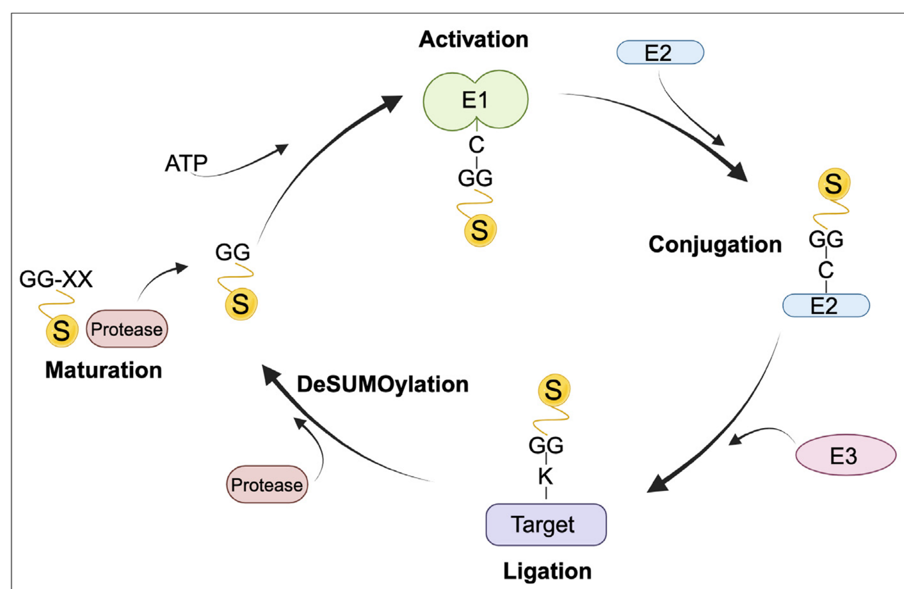

Fig. 1. The SUMOylation pathway is initiated by cleavage of a precursor SUMO into its mature form with a Gly-Gly motif. E1 activating enzymes interact with SUMO, forming an ATP-dependent thioester bond. The SUMO moiety is transferred to the E2 conjugating enzyme. E3 ligases help to facilitate the transfer of SUMO to the Lys residues of a target protein. DeSUMOylation of a protein is carried out by the action of SUMO-specific proteases.

(Jensen et al., 2001). PML SUMOylation by SUMO-1 is required for its nuclear body (condensate) localization (Shen et al., 2006). PML also contains a SIM for non-covalent binding with other SUMO substrates, and most protein partners associated with PML condensates, including DAXX, HIPK2, and SP100, are also SUMO-targeted or contain SIMs (Sung et al., 2011; Weidtkamp-Peters et al., 2008). Strikingly, disrupting the SIMs of PML results in a loss of PML condensate formation (Shen et al., 2006). This indicates that SUMO-SIM interactions drive LLPS, therefore this interaction was termed "SUMO glue" (Cheng et al., 2023; Keiten-Schmitz et al., 2021). The growing SUMO-SIM interaction network is crucial for the biogenesis of PML condensates, and very likely for many other cellular structures.

1.4. Group SUMOylation within protein assemblies

In contrast to the ubiquitin pathway, which involves many enzymes, the SUMO pathway operates with relatively few enzymes despite having a wide variety of substrates. Recent evidence indicates that SUMOylation often targets entire groups of interacting proteins rather than a single substrate, differing from typical behaviors of post-translational modifications that exhibit high substrate specificity. It has been shown that multiple proteins in the same complex are SUMOylated, and this phenomenon has been termed protein group SUMOylation (Jentsch & Psakhye, 2013). In support of this idea, multiple proteins in some complexes, such as cohesin, condensin, telomere binding proteins, and nucleolar proteins, are SUMOylated as a group in budding yeast (Albuquerque et al., 2013). Collective group SUMOylation may be initiated when the SUMO machinery, specifically SUMO E3 ligases, is recruited to established protein complexes. The best-known example of this occurrence is during double strand break (DSB) repair by homologous recombination (HR). Upon DNA damage in mammalian cells, DNA repair factors (RPA, BRCA1, 53BP1, and MDC1) become SUMOylated and colocalize with SUMO machinery (Dou et al., 2010; Luo et al., 2012; Morris et al., 2009; Yin et al., 2012). Specifically, Ubc9 and E3 ligases PIAS1 and PIAS4 localize to sites of DNA repair within subnuclear repair foci (Galanty et al., 2009; Morris et al., 2009). Studies in budding yeast also demonstrate group SUMOylation following DNA damage (Psakhye & Jentsch, 2012). This coordinated SUMOylation is triggered by the resection of DSB ends, leading to the formation of long single-stranded DNA (ssDNA) regions that attract DNA repair factors. The process of collective SUMOylation is facilitated by E3 ligase Siz2, which binds to DNA and interacts with many of its substrates (Jentsch & Psakhye, 2013). Our recent observation also supports this idea. Artificial recruitment of SUMO E2 enzyme Ubc9 to one component of the nucleolar silencing and telophase (RENT) complex in budding yeast results in the SUMOylation of other RENT components (Gutierrez-Morton et al., 2024). Since many proteins can be SUMOylated at multiple sites and these proteins and their partners often contain SIMs, group SUMOylation results in multiple SUMO-SIM interactions, which facilitates the formation of multiprotein complexes.

2. SUMOylation: key functions in cell cycle progression

SUMOylation plays a critical role in cell cycle progression, and here we focus on our understanding of SUMOylation function in yeast cells. In yeast, the singular gene encoding SUMO, *SMT3*, was initially identified as a high-copy suppressor of a temperature-sensitive *mif2* kinetochore mutant, highlighting its role in chromosome segregation (Meluh & Koshland, 1995). Indeed, cells depleted of Smt3 and temperature-sensitive *smt3* mutants show defective chromosome segregation (Biggins et al., 2001; Dieckhoff et al., 2004). Other components of the SUMO machinery, including the SUMO-conjugating enzyme Ubc9, are also indispensable, as mutations, such as temperature-sensitive *ubc9-1*, *ubc9-2*, and *ubc9-10* mutants, lead to cell cycle arrest with undivided nuclei (Betting & Seufert, 1996; Jacquiau et al., 2005; Maeda et al., 2003; Seufert et al., 1995). Yeast proteins modified by SUMO affect a variety of cellular processes, including telomere maintenance, kinetochore function, transcription regulation, nucleolar dynamics, septin organization, DNA synthesis, DNA damage repair, sister chromatid cohesion, and chromosome condensation (Abrieu & Liakopoulos, 2019; Bhachoo & Garvin, 2024; Boulanger et al., 2021; Wan et al., 2012; Yalçin et al., 2017). While the function of some SUMOylation events has been extensively studied, much remains to be defined.

2.1. SUMOylation and protein degradation

SUMOylation of specific substrates can signal their subsequent degradation, often through the action of specialized ubiquitin ligases known as SUMO-targeted ubiquitin ligases (STUbLs). One example is the degradation of the yeast protein Dbf4, the regulatory subunit of Dbf4-dependent kinase (DDK) (Psakhye et al., 2019). The DDK phosphorylates the replicative helicase MCM (minichromosome maintenance) complex to allow the initiation of DNA replication (Bell & Labib, 2016). The SUMO protease Ulp2 is enriched at replication origins and prevents Dbf4 polySUMOylation. Once DNA replication is complete, Dbf4 undergoes polySUMOylation, which is recognized by STUbL Slx5/Slx8 to trigger proteasomal degradation of Dbf4. This mechanism highlights how SUMOylation regulates DNA replication by precisely controlling the turnover of key replication factors such as Dbf4.

Another notable example of SUMO-dependent protein degradation is the nucleolar protein Tof2. The nucleolus serves as a hub for sequestering Cdc14, a phosphatase crucial for mitotic exit (Visintin et al., 1998). This nucleolar sequestration of Cdc14 relies on two nucleolar anchors, Net1 and Tof2 (Shou et al., 1999; Traverso et al., 2001; Waples et al., 2009). Interestingly, these two anchor proteins are SUMO substrates (Albuquerque et al., 2013). Recent work from our group has unveiled a cell cycle-dependent nucleolar delocalization of Tof2, which is triggered by polySUMOylation (Gutierrez-Morton et al., 2024). After induction of Tof2 polySUMOylation, we observed rapid Tof2 nucleolar delocalization and degradation. Interestingly, this delocalization and degradation depend on polySUMO-dependent ubiquitination by STUbL as well as the extraction by segregase Cdc48. Overall, the polySUMO-dependent Tof2 turnover promotes the release and activation of Cdc14 phosphatase for mitotic exit.

One further question is whether STUbL-mediated ubiquitination is sufficient for proteasomal degradation of polySUMOylated substrates. It is likely that additional E3 ubiquitin ligases are required for this degradation. For example, previous studies show that Dbf4 degradation depends on the anaphase-promoting complex, an E3 ubiquitin ligase essential for anaphase entry (Ferreira et al., 2000; Lu et al., 2014). For Tof2, our results show that polySUMOylation triggers the dissociation of Tof2 from rDNA even when its degradation is blocked by a proteasomal-deficient mutant, indicating that Tof2 dissociation from rDNA occurs before its degradation (Gutierrez-Morton et al., 2024). Therefore, it is likely that an additional E3 ubiquitin ligase is required for Tof2 degradation, although this ligase remains unknown.

2.2. SUMO and chromosome segregation

In budding yeast, many SUMO substrates are related to chromosome segregation. One of the primary targets of SUMOylation is the cohesin complex, which holds sister chromatids together until their separation during anaphase. All the subunits in the cohesion complex, as well as cohesin-associated factor Pds5, are SUMO substrates (Albuquerque et al., 2013; Stead et al., 2003). It appears that polySUMOylation promotes sister chromatid separation, and we will discuss the details of how SUMOylation regulates cohesion in Section 3.4.

SUMOylation activity at kinetochores has been extensively studied (Azuma et al., 2005; Nie et al., 2009; Zhang et al., 2008). The kinetochore is a multiprotein complex that mediates the attachment of chromosomes to microtubules, and many kinetochore proteins are SUMOylated in both yeast and human cells (Albuquerque et al., 2013; Ohta et al., 2010). The

integrity and function of the kinetochore relies on SUMO homeostasis as depletion of Ulp2 causes higher frequency of chromosome missegregation and aneuploidy. The SUMOylation level of inner kinetochore proteins, including Mcm21, Mcm16, Mcm22, Ame1, and Okp1, is elevated in cells lacking Ulp2 (de Albuquerque et al., 2016; Ryu et al., 2016; Suhandynata et al., 2019). Apart from its C-terminal SIM motif, Ulp2 contains a kinetochore-targeting motif for its specific recruitment to an inner kinetochore protein Ctf3 (Suhandynata et al., 2019). Recent studies in mammalian cells showed that SUMO protease SENP6 is essential for the assembly of inner kinetochore likely by preventing kinetochore protein polySUMOylation (Liebelt et al., 2019; Mukhopadhyay et al., 2010). The absence of SENP6 enables Cdc48/p97 segregase-dependent centromere dissociation of inner kinetochore proteins (van den Berg et al., 2023), but more work is needed to understand how SUMOylation of kinetochore proteins regulates their function in chromosome segregation.

Recent evidence in budding yeast shows that shugoshin (Sgo1), a conserved pericentromeric-localized protein critical for chromosome biorientation, is SUMOylated in a cell cycle-dependent manner (Su et al., 2021). Once sister kinetochores establish tension through biorientation, Sgo1 is SUMOylated and subsequently released from chromatin. This study showed that Sgo1 SUMOylation facilitates its pericentromeric release and degradation. In addition to Sgo1, some subunits of the chromosomal passenger complex (CPC), Bir1 and Ipl1, are also identified as SUMO targets in budding yeast (Su et al., 2021). Aurora B/Ipl1 kinase is the enzymic subunit of the CPC, and its phosphorylation of kinetochore proteins destabilizes incorrect chromosome attachment to ensure accurate chromosome segregation (Wang et al., 2014). Notably, some CPC components in mammalian cells also undergo SUMOylation (Ban et al., 2011; Klein et al., 2009). Further effort is needed to understand how SUMOylation regulates CPC function.

3. The function of mono- and polySUMOylation in condensate dynamics and protein localization

SUMOylation regulates protein stability, localization, and interaction with protein partners. While SUMO-1 in mammalian cells is generally associated with monoSUMOylation (Tatham et al., 2001), SUMO-2 and SUMO-3 (SUMO-2/3) are capable of forming polymeric SUMO chains on target proteins through acceptor lysines K11 within SUMO (Hendriks et al., 2017; Tatham et al., 2001). Some SUMO substrates rely on monoSUMOylation for localization and stability. For instance, RanGAP1, a GTPase-activating protein involved in nucleocytoplasmic transport, depends on monoSUMOylation for its nuclear pore complex targeting (Matunis et al., 1998; Saitoh & Hinchey, 2000).

Unlike monoSUMOylation, polySUMOylation serves as a unique signal to recruit additional enzymes for further ubiquitination and segregation. SUMO-targeted ubiquitin E3 ligases (STUbLs) specifically bind to polySUMO chains and ubiquitinate neighboring lysine residues. The most studied STUbLs are RNF4 and RNF111 in mammals and the Slx5/Slx8 heterodimer in budding yeast (Miteva et al., 2010; Sriramachandran et al., 2019; Tatham et al., 2008). Notably, STUbLs contain two N-terminal SIMs that recognize polySUMO chains. STUbL-mediated substrate ubiquitination subsequently triggers extraction by the segregase Cdc48/p97/VCP (Dantuma & Hoppe, 2012; Køhler et al., 2015). The Cdc48 complex, composed of six monomers each with two ATPase domains, forms a double-ring structure (Bodnar & Rapoport, 2017). Cdc48 is associated with cofactors Npl1 and Ufd1, the latter of which harbors a SIM to mediate interaction between the Cdc48 complex and SUMO substrates (Bergink et al., 2013; Bodnar et al., 2018). Thus, polySUMOylation triggers ubiquitination by STUbL and the subsequent extraction by Cdc48, ultimately causing dissolution of biomolecular condensates or protein delocalization (Lallemand-Breitenbach et al., 2008; Tatham et al., 2008). It is believed that limited SUMOylation facilitates assembly of biomolecular condensates or protein subcellular localization, but polySUMOylation reverses these processes through the polySUMO-STUbL-Cdc48 pathway. In the following sections, we will explore how polySUMOylation disrupts biomolecular condensates and delocalizes proteins.

3.1. *PolySUMOylation and PML condensates*

The dissolution of PML condensates depends on a molecular switch from mono to polySUMOylation, which promotes the recruitment of STUbL RNF4 to the condensates for proteolytic ubiquitination and disassembly (Lallemand-Breitenbach et al., 2008; Tatham et al., 2008). In fact, PML was the first protein identified to be degraded by SUMO-dependent and RNF4-mediated activity. Oxidative stress enhances SUMOylation, and treating cells with a protein-misfolding inducer arsenic trioxide has been demonstrated to induce polySUMOylation of PML (Geoffroy et al., 2010; Hattersley et al., 2011). While the initial size and number of PML condensates as well as PML SUMOylation by polySUMO-specific SUMO-2/3 increases, the condensates ultimately vanish by 16 h after arsenic treatment. In contrast, overexpression of monoSUMO-specific SUMO-1 prevents the disassembly of PML condensates. These results suggest that monoSUMOylation safeguards PML condensate integrity, but polySUMOylation triggers its dissolution.

3.2. *PolySUMOylation and ALT-associated PML nuclear bodies (APBs)*

Telomeres consist of TTAGGG repeats. With each cell division, telomeres become progressively shorter. Cancer cells develop a telomere maintenance mechanism (TMM) by reactivating telomerase activity, thereby allowing telomere elongation. However, 10%–15% of cancer cells, such as sarcomas and soft tissue tumors, rely on a TMM-independent mechanism, termed the alternative lengthening telomeres (ALT) pathway for telomere elongation (Bryan et al., 1997; Dilley & Greenberg, 2015). This pathway uses DNA recombination and repair to increase telomere length, but the detailed molecular mechanism of ALT remains elusive. One of the hallmarks of ALTs is the presence of ALT-associated PML nuclear bodies (APBs), which are a specific class of PML condensates localized on telomeric DNA (Lallemand-Breitenbach & de Thé, 2010; Yeager et al., 1999). These condensates sequester a wide array of proteins involved in tumor suppression, DNA repair, and apoptosis. The biogenesis of APBs relies on PML, as knockdown of PML protein results in abolished APB formation and telomere shortening (Draskovic et al., 2009). Similar to canonical PML condensates, APBs are also dependent on the multivalent SUMO-SIM interactions between PML proteins and associated partners (Banani et al., 2017; Potts & Yu, 2007; Zhang et al., 2020). Uniquely, APBs disassemble during late mitosis, and disruption in SUMO-SIM interactions leads to ABP dissolution. Since polySUMOylation increases during mitosis, the hyper polySUMOylated state of APBs may alter the liquid properties of the condensates, triggering their disassembly (Min et al., 2019). Alternatively, APB polySUMOylation may trigger its dissolution through the polySUMO-STUbL-Cdc48 pathway.

3.3. *PolySUMOylation and DNA damage response*

SUMOylation plays a critical role in the cellular DNA damage response by regulating the formation and disassembly of nuclear condensates at DNA damage sites. In budding yeast, DNA damage leads to the formation of liquid droplets/condensates at the damage sites, which include DNA damage repair protein Rad52 (Oshidari et al., 2020). These condensates serve as concentrated hubs where repair proteins can rapidly assemble and coordinate the repair process.

In mammalian cells, SUMOylated DNA damage response (DDR) proteins also accumulate at DNA damage sites as nuclear condensates (Alghoul et al., 2023; Wang et al., 2022). Following genotoxic stress, the STUbL is recruited to polySUMOylated proteins within these condensates, facilitating their proteolytic or nonproteolytic ubiquitination and

Table 2
Identified yeast and human SUMO substrates localized in condensates.

Identified SUMO target (Gene Names)		
Condensate	*S. cerevisiae*	*H. sapiens*
PML nuclear bodies	None	PML (Tatham et al., 2008), SP100 and TDG (Sahin et al., 2014), DAXX (Lin et al., 2006), HIPK2 (Sung et al., 2019), p53 (Ivanschitz et al., 2015), CBP (Ryan et al., 2010), ATRX (Correa-Vázquez et al., 2021), MRE11 (Sohn & Hearing, 2012)
ALT-associated PML bodies (APBs)	None	TRF1 (Yu et al., 2007), TRF2 (Zhang et al., 2021), RPA (Dou et al., 2010), MRE11 (Sohn & Hearing, 2012), WRN (Kawabe et al., 2000), BRCA1 (Vialter et al., 2011), XRCC3 (Hu et al., 2018), PRB (Ledl et al., 2005), TPZ1 (Garg et al., 2014), 53BP1 (Galanty et al., 2009), RIF1 (Kumar & Cheok, 2017), HNRNPA2 (Vassileva & Matunis, 2004), HP1A, HP1B and HP1γ (Maison et al., 2016), ATM and ATR (Munk et al., 2017), FANCA and FANCD2 (Coleman & Huang, 2016), SLX4 and FEN1 (Yalçin et al., 2017), γ-H2AX (Chen et al., 2013), MDC1 (Luo et al., 2012), MUS81 (Hu et al., 2017), NXP2 (Mimura et al., 2010), PARP1 (Zilio et al., 2013), POT1 (Singh et al., 2013), RAD51 (Shima et al., 2013), RAD52 and PCAN (Silva et al., 2016), BLM (Min et al., 2019), SMC5/6 (Varejão et al., 2018), TOPOIIA (Ryu et al., 2010), PML (Sahin et al., 2014), p53 (Schmidt & Müller, 2002), SP100 (Guion et al., 2019), DAXX (Jang et al., 2002), RAP1 (Chymkowitch et al., 2015)
DNA damage foci	Rfa1, Rad59 (Burgess et al., 2007), Sgs1, Top3 (Bonner et al., 2016), Top2 (Yoshida & Azuma, 2016), H2A.Z and Yku70/Yku80 (Kalocsay et al., 2009), PCNA (Li et al., 2018), Yen1 (Talhaoui et al., 2018), Rad52 (Su et al., 2015), Srs2 (Kramarz et al., 2017), DDK (Psakhye et al., 2019), Mms4 (Waizenegger et al., 2020)	PCNA (Gali et al., 2012), BRCA1 (Vyas et al., 2013), RPA1 (Galanty et al., 2012), 53BP1 (Groocock et al., 2014), XRCC4 (Yurchenko et al., 2006), XRCC5 (Kumar et al., 2017), KU70/KU80 (Yurchenko et al., 2008), RAD51 (Hariharasudhan et al., 2022), MDC1 (Galanty et al., 2012), FANCA (Xie et al., 2015), FANCE (Xie et al., 2015), FANCD2 (Gibbs-Seymour et al., 2015), BLM (Kumar et al., 2017), RAD18 (Kumar et al., 2017), ERCC1 (Guervilly et al., 2015), SLX4 (Guervilly et al., 2015), RAP1 (Chymkowitch et al., 2015), KAP1 (Bürck et al., 2015), CTIP (Locke et al., 2021)
Nucleolus	Tof2, Net1, Cdc14 (de Albuquerque et al., 2016; Liang et al., 2017), Fob1 (Gillies et al., 2016), Sir2 (Hannan et al., 2015), Nur1 (Capella et al., 2021), Lrs4 (Capella et al., 2021)	DKC1 (Manza et al., 2004; Westman et al., 2010), NHP2 (Blomster et al., 2009; Westman et al., 2010), NOLC1 (Golebiowski et al., 2009; Westman et al., 2010), NOP58 (Westman et al., 2010; Westman & Lamond, 2011), DDB2 (Vertegaal et al., 2006; Westman et al., 2010), DDX21 (Matafora et al., 2009; Westman et al., 2010), TFRC and NFIX (Golebiowski et al., 2009; Westman et al., 2010), ALPL ALPP, CAV1, CYB5B, PDLIM7, KLHDC3, FHL1, PRMT5, LSS, RDH10, and EXOSC10 (Westman et al., 2010).

condensate dissolution. This process is crucial for maintaining genome stability during DSB repair, non-homologous end joining, homologous recombination, and DNA replication stress (Chang et al., 2021). Many DDR factors, including BRCA1-BARD1, MDC1, RPA70, SLX4, FANCI, and FANDC2, are SUMO substrates, and SUMO protease SENP6 retains their hypoSUMOylated status. Depletion of SENP6 causes their poly-SUMOylation and the recruitment of STUbL RNF4 (Claessens et al., 2023), which likely contributes to condensate disassembly. Additionally, recent evidence suggests that SLX4, a scaffolding protein and component of structure-specific endonucleases involved in DNA repair, is SUMO-targeted and utilizes SUMO-SIM interactions to drive condensate biogenesis in response to DNA damage (Alghoul et al., 2023). Like other DNA-repair factors, the disassembly of SLX4 condensates is facilitated by STUbL activity.

3.4. PolySUMOylation and cohesin complexes

After DNA replication, all eukaryotic cells rely on cohesion to hold sister chromatids together until anaphase onset. The cohesin complex is a ring-shaped ATPase that topologically interacts with chromosomes and is crucial for accurate chromosome segregation (Uhlmann, 2016). A recent study in budding yeast demonstrated the dynamic assembly of cohesin with DNA, consistent with condensate biogenesis (Ryu et al., 2021). Furthermore, DNA-cohesin clusters exhibit liquid-like behavior that is dependent on DNA length, a feature that is characteristic of phase separation.

All four cohesin subunits and a cohesion-associated factor Pds5 are targets for SUMOylation in yeast cells, which occurs concurrently with cohesion establishment during DNA replication (Almedawar et al., 2012; McAleenan et al., 2012). Depletion of SUMO protease in yeast cells reduced cohesin binding to DNA (Wagner et al., 2019). It was further demonstrated that the cohesin regulator Pds5 recruits SUMO protease Ulp2 to protect cohesin subunits from premature polySUMOylation and the subsequent ubiquitination by the STUbL heterodimer Slx5/Slx8 (Psakhye & Branzei, 2021). These findings suggest that the multivalent SUMO-SIM interactions mediated by limited SUMOylation drive cohesin condensate formation to facilitate cohesion establishment. In addition, the absence of Pds5 or SUMO protease Ulp2 leads to premature sister chromatid separation (Bachant et al., 2002; Hartman et al., 2000). In budding yeast, polo-like kinase Cdc5 phosphorylates Ulp2, which likely inactivates Ulp2. Interestingly, hyperactive Cdc5 also leads to premature sister chromatid separation (Baldwin et al., 2009). One explanation is that polySUMOylation triggers the disassembly of the cohesin condensate and facilitates sister cohesion dissolution.

3.5. PolySUMOylation and the localization of nucleolar proteins

The nucleolus is a subnuclear biomolecular condensate primarily responsible for ribosome production (Correll et al., 2019). Numerous proteins within the nucleolus have been identified as SUMO substrates (Westman et al., 2010), prompting the idea that SUMOylation may modulate the localization of nucleolar proteins. Recently, we have demonstrated a polySUMO-dependent nucleolar release and degradation of Tof2, a nucleolar anchor for Cdc14 phosphatase, thereby revealing the role of polySUMOylation in Cdc14 activation and mitotic exit

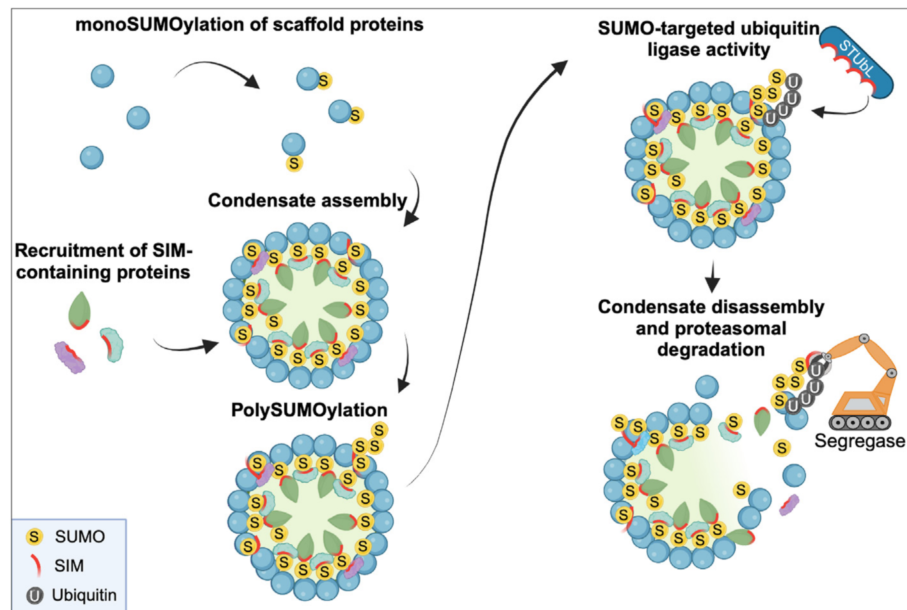

Fig. 2. PolySUMOylation triggers condensate disassembly. SUMO-SIM interactions drive phase separation and condensate assembly. PolySUMOylation is a signal for ubiquitination by SUMO-targeted ubiquitin ligases (STUbLs) and segregation by Cdc48 segregase, causing condensate disassembly and protein turnover.

(Gutierrez-Morton et al., 2024). Additionally, polySUMOylation is involved in releasing membrane-tethered rDNA from the nucleolus following rDNA damage in budding yeast (Capella et al., 2021). The chromatin linkage of inner nuclear membrane proteins (CLIP) and the Cohibin complex tether rDNA to the nuclear envelope. Two Lrs4 proteins and two Csm1 homodimers make up the "V"-shaped Cohibin complex, which physically link to CLIP proteins Heh1 and Nur1 (Huang et al., 2006; Mekhail et al., 2008). The movement of damaged rDNA repeats from the nucleolus to the nucleoplasm is essential for their repair. Interestingly, this movement is facilitated by the polySUMOylation of CLIP-cohibin components Nur1 and Lrs4. The CLIP-cohibin complexes modified by polySUMO chains are recognized by segregase Cdc48 through its substrate-recruiting co-factor Ufd1, which harbors a SIM (Bergink et al., 2013). Thus, polySUMOylation enables the movement of rDNA repeats away from the nucleolus for their repair after rDNA damage. The list of SUMOylated proteins in known condensates is shown in Table 2.

4. SUMOylation-related diseases

Given the role of SUMOylation in protein localization, stability, and function, this posttranslational modification has significant implications in most cellular processes (Celen & Sahin, 2020). Because mono- and polySUMOylation play distinct roles, the coordinated actions of SUMOylation enzymes and SUMO proteases are critical to control the balance between SUMO chain accumulation and deconjugation. Abnormal SUMOylation dynamics can lead to cancers, neurodegenerative diseases, and other disorders. Notably, many diseases linked to SUMOylation show aberrant forms of phase-separated condensates (Alberti & Dormann, 2019).

4.1. The role of SUMOylation in cancer development and treatment

A variety of oncogenes and tumor suppressors are SUMO substrates, and in many cases, hyper SUMOylation is linked to cancer development. This can be best exemplified in MYC-dependent tumorigenesis. MYC is an oncogenic transcription factor, and its monoSUMOylation causes stabilization and enhanced transcriptional dysregulation, both of which promote cancer development and metastasis (Hoellein et al., 2014; Kessler et al., 2012). Recent evidence shows that condensate formation is critical for transcriptional regulation (Boehning et al., 2018; Boija et al., 2018; Cho et al., 2018). Thus, MYC monoSUMOylation may drive aberrant transcription by facilitating transcriptional condensate formation. PML is a well-characterized SUMO substrate, and its dysfunctional mutations are associated with cancer development, and the mutant phenotypes are coincident with alterations to PML condensates (Zhao et al., 2019).

Since SUMOylation is often upregulated in most cancers, significant efforts have been made for the discovery of new anti-cancer treatments targeting the SUMO conjugation pathway, including E1 and E2 SUMO enzyme inhibitors. Ginkgolic acid and anacardic acid, for example, bind to SUMO E1 and inhibit SUMOylation in vitro (Fukuda et al., 2009). Furthermore, treating cancer cell lines with ML-792, a highly specific and effective E1 inhibitor, reduces cell viability and decreases MYC expression (He et al., 2017). However, considering the thousands of SUMO substrates identified, targeting specific, pro-oncogenic SUMOylation events rather than global SUMOylation remains imperative for an effective therapeutic strategy. APL, or acute promyelocytic leukemia, is a subtype of acute myeloid leukemia involving the expression of the oncogenic PML-retinoic acid receptor alpha (RARA) fusion protein (Borrow et al., 1990). Arsenic trioxide is a widely used treatment to combat APL as this compound targets this oncoprotein for degradation via the polySUMO-triggered and STUbL-mediated pathway (Lallemand-Breitenbach et al., 2008).

4.2. Neurodegenerative diseases

Neurodegenerative diseases are characterized by their progressive impairment of cognitive function, including Alzheimer's disease, Huntington's disease, Parkinson's disease, etc. A common feature of neurodegeneration is the aberrant aggregation of cytosolic or nuclear proteins (Folger & Wang, 2021; Taylor et al., 2002). Notably, many proteins comprising these pathological protein aggregates are targets of SUMO. Therefore, SUMOylation plays a critical role in driving neurodegeneration. For example, in Alzheimer's and Parkinson's disease, the microtubule-binding protein tau is expressed in the brain at high levels, forming cytosolic aggregates (Grundke-Iqbal et al., 1986). Tau undergoes monoSUMOylation, which promotes its aggregation (Dorval & Fraser, 2006). Specifically, fusing tau to SUMO-1 triggers its oligomerization

(Takamura et al., 2022). This suggests that monoSUMOylation facilitates the formation of cytotoxic tau assemblies and the pathogenesis of Alzheimer's disease.

Huntington's disease is caused by oligomerization of mutant huntingtin protein, which is characterized by an expansion of CAG trinucleotide in this gene, causing an increase of the polyglutamine (polyQ) repeat (Orr & Zoghbi, 2007; Walker, 2007). The repetitive sequences participate in multivalent interactions, inducing condensate assembly of mutant huntingtin (Zu et al., 2011). Mutant huntingtin protein is also a known SUMO substrate, modified by both SUMO-1 (monoSUMOylation) and SUMO-2 (polySUMOylation). Modification by SUMO-1 is linked with increased stability and solubility of mutant huntingtin (Steffan et al., 2004; Subramaniam et al., 2009). Interestingly, SUMO-2 modification of mutant huntingtin results in insoluble protein aggregates, which is related to pathogenesis (O'Rourke et al., 2013). Reduced global SUMOylation levels were found to slow down neurodegeneration progression (Steffan et al., 2004). However, more work is needed to define the precise roles of mono- and polySUMOylation in the aggregation and degradation of mutated huntingtin, which will likely provide viable strategies for treating protein aggregation diseases.

5. Concluding remarks

SUMOylation is an essential post-translational modification, functioning in numerous cellular processes. SUMO moieties are reversibly attached to lysine residues, affecting the stability, localization, and interaction networks of many substrates. Recent studies support an overarching model that limited SUMOylation promotes biomolecular condensate assembly or protein subcellular localization through SUMO-SIM interactions, however, polySUMOylation facilitates condensate disassembly as well as protein delocalization and turnover (Fig. 2). Therefore, SUMOylation is critical to regulate protein subcellular localization and function. Future work is needed to understand the function of this modification in different biological processes in the temporal and spatial context. One important question is how cells control the transition from monoSUMOylation to polySUMOylation, which play distinct roles in protein subcellular localization. Understanding the function and regulation of SUMOylation may reveal potential therapeutic targets for combatting cancers and other diseases.

CRediT authorship contribution statement

Emily Gutierrez-Morton: Writing – review & editing, Writing – original draft, Conceptualization. **Yanchang Wang:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Yanchang Wang reports financial support, administrative support, article publishing charges, equipment, drugs, or supplies, and travel were provided by the National Institutes of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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