Safeguarding genome integrity with small ubiquitin-like modifiers

Claessens, L.A.

Chapter 2

SUMO proteases: from cellular functions to disease

Laura A. Claessens, Alfred C.O. Vertegaal

Department of Cell & Chemical Biology, Leiden University Medical Center, Leiden, The Netherlands

Published in Trends in Cell Biology, 2024
doi.org/10.1016/j.tcb.2024.01.002

ABSTRACT

Posttranslational modification by small ubiquitin-like modifiers (SUMOs) is critical in regulating diverse cellular processes including gene expression, cell cycle progression, genome integrity, cellular metabolism, and inflammation and immunity. The covalent attachment of SUMOs to target proteins is highly dynamic and reversible through the concerted action of SUMO conjugating and deconjugating enzymes. In mammalian cells, sentrin-specific proteases (SENPs) are the most abundant family of deconjugating enzymes. This review highlights recent advances in our knowledge of the substrates and cellular and physiological processes controlled by SENPs. Notably, SENPs are emerging as significant players in cancer, as well as in other diseases, making them attractive targets for therapeutic intervention. Consequently, a growing amount of effort in the field is being directed towards the development of SENP inhibitors.

Keywords: posttranslational modification, SUMO, SUMO protease, SENP, cancer

Highlights

- In recent years, more substrates and cellular and physiological processes under the control of sentrin-specific proteases (SENPs) have been revealed. SENPs play important roles in gene expression, cell cycle progression, genome stability, cellular metabolism, macromolecular assemblies, and infection and immunity.
- SENPs have emerged as important players in tumorigenesis and as potential therapeutic targets in cancer. SENPs are frequently overexpressed in cancer and are associated with poor prognosis and resistance against anticancer drugs.
- Besides cancer, the dysregulation of SENPs has been linked to other diseases, including cardiac, metabolic, muscular, and neurological conditions.
- Because of their therapeutic potential in cancer and other diseases, increasing effort has been put into the discovery and development of SENP inhibitors.

BALANCING THE SUMO SYSTEM THROUGH CONJUGATION AND DECONJUGATION

SUMOs are members of the ubiquitin-like protein family and function as posttranslational modifiers of a large number of proteins. SUMOs are covalently attached to lysine residues in the target proteins in an ATP-dependent enzymatic cascade, involving the SUMO E1 activating enzyme (SAE1/UBA2), the SUMO E2 conjugating enzyme UBC9, and SUMO E3 ligases (Figure 1A) [1]. SUMOs are translated as inactive precursors and processed into mature SUMOs by SUMO proteases [2, 3, 4]. Mammalian cells encode four SUMO isoforms. SUMO1 shares ~50% sequence identity with SUMO2 and SUMO3. SUMO2 and SUMO3 are nearly identical and are often referred to as SUMO2/3. SUMO4 does not appear to be processed by SUMO proteases and is therefore thought to be nonconjugatable [5]. SUMOs are predominantly present in the nucleus and are essential for a variety of processes, including progression of the cell cycle, genome stability, and transcription (reviewed in [1]).

SUMOylation can result in the modification of a single (monoSUMOylation) or multiple lysine residues (multi-monoSUMOylation) in the target proteins (Figure 1B). Through internal lysine residues in SUMOs, SUMOylation by SUMO2/3 can also give rise to polymeric chains (**polySUMOylation**)(see Glossary). Additionally, SUMO1 chains are likely to exist [6,7]. The SUMOylation of proteins can affect their stability, activity, localisation, and noncovalent interaction with other proteins through **SUMO interaction motifs (SIMs)** [8]. Polymeric SUMO chains on proteins can be recognised by **SUMO-targeted ubiquitin ligases (STUbLs)**, such as RNF4 and RNF111, which subsequently ubiquitinate the protein and target it for proteasomal degradation or nonproteolytic signalling events (Figure 1C) [9].

SUMOylation is a highly dynamic and reversible process. The deconjugation of SUMOs is achieved by SUMO proteases. These enzymes are key players in balancing the level of SUMO modification in cells by regulating both the maturation of SUMOs prior to conjugation and by removing SUMOs from the substrates (Figure 1A).

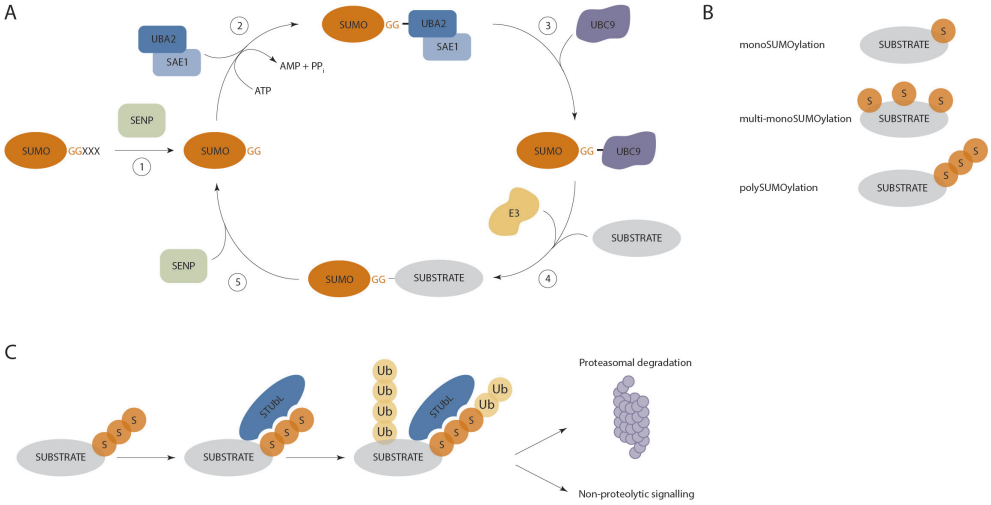

Figure 1. Balancing the small ubiquitin-like modifier (SUMO) system through conjugation and deconjugation. (A) In mammalian cells, SUMOs are translated as inactive precursors and processed into mature SUMOs by sentrin-specific proteases (SENPs) (1). The maturation of SUMOs involves hydrolyzation of a peptide bond at the SUMO C terminus, which exposes a diGly (GG) motif that forms a thioester bond with the SUMO E1 enzyme (SAE1/UBA2) in an ATP-dependent manner (2). The SUMO is then transferred to the catalytic cysteine residue of the SUMO E2 enzyme UBC9 via transthiolation (3). Subsequently, UBC9 conjugates the SUMOs to lysines in the substrates with or without the help of SUMO-E3-ligating enzymes (4). SUMOs can be deconjugated from the substrates by SENPs, facilitating the recycling of SUMOs (5). (B) SUMOs can be conjugated to a single lysine residue of a protein (monoSUMOylation) or to multiple lysine residues (multi-monoSUMOylation), or form SUMO chains (polySUMOylation). (C) Polymeric SUMO chains on proteins can be recognised by SUMO-targeted ubiquitin ligases (STUbLs), which subsequently ubiquitinate the protein and target it for proteasomal degradation or nonproteolytic signalling events. Abbreviations: AMP, adenosine monophosphate; PP_i, inorganic pyrophosphate; S, SUMO; SAE1, SUMO-activating enzyme subunit 1; STUbL, SUMO-targeted ubiquitin ligase; Ub, ubiquitin.

MATURATION AND DECONJUGATION OF SUMOS BY SUMO PROTEASES

The first SUMO proteases to be described were the UbL-specific proteases 1 and 2 (Ulp1, Ulp2) in yeast [10,11]. The mammalian SENP family was discovered later through their sequence similarity to the Ulp family and consists of six SUMO proteases, SENP1–3 and SENP5–7 [2]. More recently, the SUMO proteases desumoylating isopeptidase 1 (DESI1), DESI2, and USPL1 were discovered, which share little sequence identity with the Ulp/SENP family [12,13]. In the past decade, no progress has been made regarding the DESIs.

Furthermore, the function of USPL1 in Cajal bodies described to date is independent of its SUMO protease activity [12,14]. The structure of USPL1 bound to SUMO2 was revealed recently, to gain a better insight into this unique specificity for SUMO for a member of the ubiquitin-specific proteases (USPs). In this review, we mainly focus on the more studied and better characterised Ulp/SENP family.

All Ulp/SENPs consist of an *N*-terminal noncatalytic region that regulates their intracellular localisation (Figure 2). In yeast Ulp2 and several SENPs, these regions also contain putative SIMs. Recently, eight putative SIMs were identified in the *N*-terminal region of SENP6 and were shown to be involved in binding to SUMO2/3 chains [15]. Ulp/SENPs are cysteine proteases consisting of a His–Asp–Cys catalytic triad. Deconjugation by SENPs involves cleavage of the isopeptidase bond between the SUMO and the lysine residue. The maturation of SUMOs involves hydrolysis of a peptide bond at the C terminus at SUMO, which exposes a diGly motif required for its activation and conjugation. The catalytic domains of SENP1–3 and -5 resemble Ulp1, whereas the catalytic domains of SENP6 and SENP7 resemble Ulp2 and form a distinct subclass. The catalytic domains of SENP6 and -7 have four conserved loop insertions that are not present in the other SENPs, which are thought to contribute to their SUMO isoform specificity and preference for cleaving SUMO2/3 chains [16].

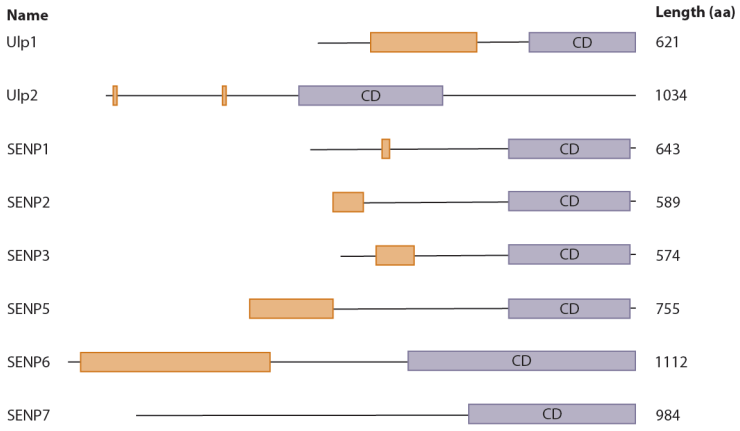

Figure 2. Structures of the Ulp/sentrin-specific protease (SENP) family of small ubiquitin-like modifier (SUMO) proteases. The domain organisations and lengths (in amino acids, aa) of the Ulp/SENP family members are shown. The catalytic domains (CD) are shown in purple. Regions that are involved in the subcellular localisation of the protein are shown in orange. The catalytic domains of SENP1–3 and-5 resemble Ulp1, whereas the catalytic domains of SENP6 and SENP7 resemble Ulp2 and form a distinct subclass.

Members of the SENP family differ in their subcellular localisation, isoform preference, and ability to process the precursor SUMO and SUMO2/3 chains (Table 1) [3,4,17]. SENP substrate specificity appears to be strongly influenced by their subcellular localisation. An illustrative example includes SENP3 and SENP5, which localise to the nucleolus and were recently shown to play an important role in the 40S and 60S ribosome maturation pathways through deSUMOylation of ribosome biogenesis factors [18]. For a more in-depth background discussion, as well as information on the regulation of SUMO proteases, we refer to earlier reviews, as they remain current with the limited recent advances on these topics [3,4,17]. In this review, we first discuss novel discoveries related to the substrates, and the cellular and physiological roles of the Ulp/SENP family. We then focus on the recent emergence of SENPs as key players in the pathogenesis of human disease, including in cancer, and the potential for therapeutic targeting with SENP inhibitors.

Table 1 | Properties of the Ulp/SENP family

Name	Subcellular localization	Isoform preference	Precursor processing	Deconjugation	Chain editing	Phenotype of knockout mice
Yeast						
Ulp1	Nuclear pore	Smt3	Yes	Yes	No	-
Ulp2	Nucleoplasm	Smt3	No	Yes	Yes	-
Mammals						
SENP1	Nuclear pore Nuclear foci[a] Kinetochore (mitosis)	SUMO1 > SUMO2/3	Yes	Yes	No	Embryonic letahility [82][c]
SENP2	Nuclear pore Nuclear foci[a] Kinetochore (mitosis)	SUMO2/3 > SUMO1	Yes	Yes	No	Embryonic lethality [19][d]
SENP3	Nucleolus Mitochondria[b]	SUMO2/3	Unknown	Yes	No	Embryonic lethality [83]
SENP5	Nucleolus Mitochondria[b]	SUMO2/3	Yes	Yes	No	NA[e]
SENP6	Nucleoplasm Chromatin[b]	SUMO2/3	No	Yes	Yes	Embryonic lethality [84]
SENP7	Nucleoplasm Chromatin[b]	SUMO2/3	No	Yes	Yes	Embryonic lethality [85]

a Partially overlapping with promyelocytic leukemia (PML) bodies
b Subfractions
c Placental labyrinth defects, severe anemia, defective erythropoiesis
d Abnormal trophoblast maturation
e NA, not available

SELECTED CELLULAR AND PHYSIOLOGICAL ROLES OF SUMO PROTEASES

GENE EXPRESSION

Gene expression is regulated by SUMO conjugation of chromatin-modifiers and transcription factors. SUMOylation commonly results in the recruitment of transcriptional repressors and gene inactivation. DeSUMOylation by SENPs counteracts this process, leading to gene activation. The SUMOylation of CBX4, a polycomb repressive complex 1 (PRC1) subunit, mediates its recruitment to the promoters of the target genes of PcG, leading to transcriptional repression, while deSUMOylation by SENP2 counteracts this process [19]. A more recent example of SENP-mediated transcriptional activation is that of the master transcription factor, c-Myc, which regulates the expression of genes involved in a plethora of cellular processes. C-Myc is modified by SUMO, and recent research has also revealed its regulation by deSUMOylation. SENP1 interacts with and deSUMOylates c-Myc, and promotes its stability and transcriptional activity in a ubiquitin- and proteasome-dependent manner [20].

In yeast, another mode of regulation was recently uncovered, in which Ulp2 is recruited to highly transcribed genes and promotes transcription by directly targeting transcription elongation by RNA polymerase II (RNAPII) [21]. By removing (poly)SUMO from histones, Ulp2 facilitates Ctk1 nucleosome association with RNAPII and its subsequent elongation. Interestingly, multiple histone subunits were identified as SENP6 targets, including the mammalian Ulp2 homolog, as well as RNAPII itself [22]. In this regard, it is tempting to speculate about the potential role for SENP6 in transcriptional regulation in mammalian cells, although this warrants in-depth investigation.

Occasionally, SENP-mediated deSUMOylation facilitates gene inactivation. An early example of this is the negative regulation of Wnt signalling by SENP1 (reviewed in [4]). Various instances of SENP-mediated transcriptional repression have been described since then. Like SENP2, SENP3 was shown to regulate silencing by PRC1, but rather than counteracting its SUMO-mediated transcriptional repression like SENP2 does, it is required for this function. SENP3 deSUMOylates several **rixosome** subunits that are required for the association of the rixosome and the PRC1 complex, thereby facilitating the silencing of PcG target genes mediated by rixosome–PRC1 [23]. These observations emphasise the versatility of gene regulation by SENPs.

RNA PROCESSING

Initially, SENPs were primarily associated with the regulation of RNA at the transcriptional level. However, recent findings have also suggested their involvement in RNA processing. In addition to the classical role of E2F1 as a transcription factor, it was identified as a regulator of the alternative RNA splicing of a large group of E2F1 target genes that are poor transcription targets, including the SUMO-chain-editing protease SENP7 [24]. Alternative splicing of SENP7, in turn, affected E2F1 target gene transcription through HP1 binding, which was previously known to suppress E2F1 transcription. Other newfound roles in RNA processing are the regulation of m(6)A mRNA by SENP1, and 3' end cleavage of small nuclear RNA by USPL1 and SENP6 [25,26].

PROGRESSION OF THE CELL CYCLE

The critical role of timely SUMO-based conjugation and deconjugation in the progression of the cell cycle was first established in yeast. Accordingly, the depletion or overexpression of SENPs is associated with cell cycle defects (SENP1, SENP2, SENP5, and SENP6; reviewed in [4,17]), although the specific substrates that are involved remain largely unclear.

At present, a well-characterised example of control of the cell cycle by SENPs is the regulation of **constitutive centromere-associated network (CCAN)** proteins and CENP-A by SENP6 at the **kinetochore**. Early evidence of the role of SENPs at the kinetochore came from observations that SENP1 and SENP2 localise to the kinetochore during mitosis (Table 1), and that overexpression of SENP2 causes a prometaphase arrest through the mislocalisation of CENP-E [27,28]. A role for SENP6 in assembly of the kinetochore was first postulated about a decade ago and has been solidified by more recent studies. Depletion of SENP6 leads to defects in **chromosome congression**, **spindle assembly**, and mitotic progression [22,29]. DeSUMOylation by SENP6 is critical for the localisation of CENP-A, CENP-H, CENP-I, CENP-K, CENP-T, CENP-C, and CENP-W at the centromeres during mitosis [22,29, 30, 31]. Loss of SENP6 results in polySUMOylation of CCAN proteins, indicating that these proteins are direct targets of SENP6. On the contrary, CENP-A stability and localisation are regulated indirectly through SENP6 by deSUMOylation of Mis18BP1 [22,31]. More recently, it was shown that the loss of SENP6 first leads to a loss of the CCAN, followed by a loss of centromeric CENP-A, and that this is mediated via the ATP-dependent **segregase p97/VCP** in a SUMO-dependent manner [32]. In yeast, the SENP6 homolog Ulp2 is recruited to the inner kinetochore via a direct interaction with Ctf3/CENP-I, followed by selective targeting of the CCAN via its SIM [33,34]. However, there is currently no evidence for SENP6 localisation to the centromere.

The SUMO protease SENP3 also plays a distinct role during the cell cycle. During mitosis, CDK1 and PP1α regulate the phosphorylation of SENP3 [35]. More recently, p53 was identified as the upstream regulator of SENP3 phosphorylation under genotoxic stress, inhibiting the activation of CDK1 and subsequently inhibiting the phosphorylation of SENP3 [36]. This regulation is crucial for the control of DNA-damage-induced G2 checkpoint signalling.

A novel and striking example of regulation of and by a SUMO protease in progression of the cell cycle was discovered recently [37]. Upon mitotic entry, the amount of lactate in cells peaks. Lactate binds to and inhibits the activity of SENP1 by forming a complex with zinc in the active site. This inhibition facilitates the SUMOylation of APC4 and remodelling of the **APC/C complex**. This remodelling drives UBE2C to bind to the complex and the subsequent degradation of cyclin B and **securin**, thus ensuring efficient and timely mitotic exit. We have described before that the SUMOylation of APC/C regulates the metaphase to anaphase transition during mitosis [38, 39, 40]. Further investigations are required to determine whether there are other cell cycle-related targets of SENP1 under the control of lactate or whether this mode of SENP1 regulation is relevant to other physiological processes where substantial amounts of lactate are produced.

INTEGRITY OF THE GENOME

Many proteins become SUMOylated in response to DNA damage, and there is an increased presence of conjugated SUMO2/3 at sites of DNA damage [41] (reviewed in [42]). DeSUMOylation by SENPs is also pivotal for maintaining genome integrity. In response to DNA damage, SENP7 is required for the relaxation of chromatin for **homologous recombination (HR)** [43]. SENP7 removes SUMO2/3 from KAP1 and facilitates the interaction of the chromatin remodeller CDH3 with chromatin. The deSUMOylation of MRE11 by SENP3 is required for the timely degradation of MRE11 and its removal from chromatin after DNA end resection [44]. Interestingly, knockdown of SENP3 led to an increase in the SUMOylation of MRE11 and a concomitant decrease in the ubiquitination of MRE11, preventing its degradation. In this case, SUMOylation of MRE11 antagonises its ubiquitination, and the knockdown of SENP3 exacerbates this effect. This is in contrast to the STUbL pathway, where multi-monoSUMOylation or polySUMOlation of a substrate facilitates its ubiquitination by a STUbL, suggesting that there are different modes of SUMO–ubiquitin crosstalk for individual SENPs and substrates. MRE11 appears to be mainly mono- and di-SUMOylated under physiological conditions, which could explain these different outcomes [44].

SENP2 was found to have a dual role in the repair of double-strand breakage. Knockdown of SENP2 led to a reduction in the efficiency of repair by both HR and **nonhomologous**

end-joining (NHEJ) in endonuclease reporter assays. During NHEJ, the timely dissociation of SENP2 from the DNA repair protein MDC1 allows for its SUMOylation and subsequent clearance through RNF4-VCP. During HR, SENP2 functions in an indirect fashion by continuously supplying and redistributing the pool of free SUMO2/3 for conjugation [45]. In line with this, knockdown of SENP6, which leads to excessive SUMO2/3 polymerisation on its substrates, also reduced the efficiency of repair by HR, which could be rescued by the supply of SUMO2/3 [43].

Similar to SENP2 and MDC1, SENP6 also maintains nuclear and genomic integrity by directly targeting the proteins involved in these processes. A role of SENP6 in the DNA damage response was first revealed by reports on individual proteins, demonstrating the deSUMOylation of the repair factors EXO1, RPA70, and the **Fanconi anaemia ID complex** by SENP6 [46, 47, 48]. More recently, two independent large-scale proteomic screens provided an extensive landscape of SENP6 substrates and revealed a wide array of proteins involved in processes such as DNA repair and replication stress [15,22]. Along with numerous other recent studies, both our group and others have continued to unveil the diverse regulation of nuclear integrity by SENP6 (Box 1 and Figure 3).

CELLULAR METABOLISM

SUMO predominantly functions in the nucleus, but its roles outside the nucleus are continuing to emerge. The SUMO protease SENP5 has a nucleolar localisation but can also be found in the mitochondria during mitosis. A GTPase involved in **mitochondrial fission**, DRP1, was identified as a substrate of SENP5 over a decade ago [49] (reviewed in [4]). Like SENP5, SENP3 has a predominantly nucleolar localisation, but is also found in the mitochondria. During **mitophagy**, a process removing aged and damaged mitochondria, SENP3 is stabilised by downregulation of the E3 ubiquitin ligase CHIP and deSUMOylates Fis1, which is required for mitochondrial fission [50].

Mitochondria are also important sensors of metabolic stress. Two examples of a role for SENPs in this process have emerged recently. SENP1 localises to the nuclear pores and foci, but accumulates in the mitochondria in mouse cells under fasting conditions, and deSUMOylates and activates Sirt3, a mitochondrial NAD-dependent deacetylase, facilitating metabolic adaption [51]. Mitochondrial-localised SENP2 is acetylated and activated under conditions of nutrient stress. SENP2 deSUMOylates SDHA and impairs assembly of the SDH complex, thereby dampening the tricarboxylic acid cycle and oxidative phosphorylation [52]. More research is required to further unravel the localisation and function of SENPs in the mitochondria and the substrates involved.

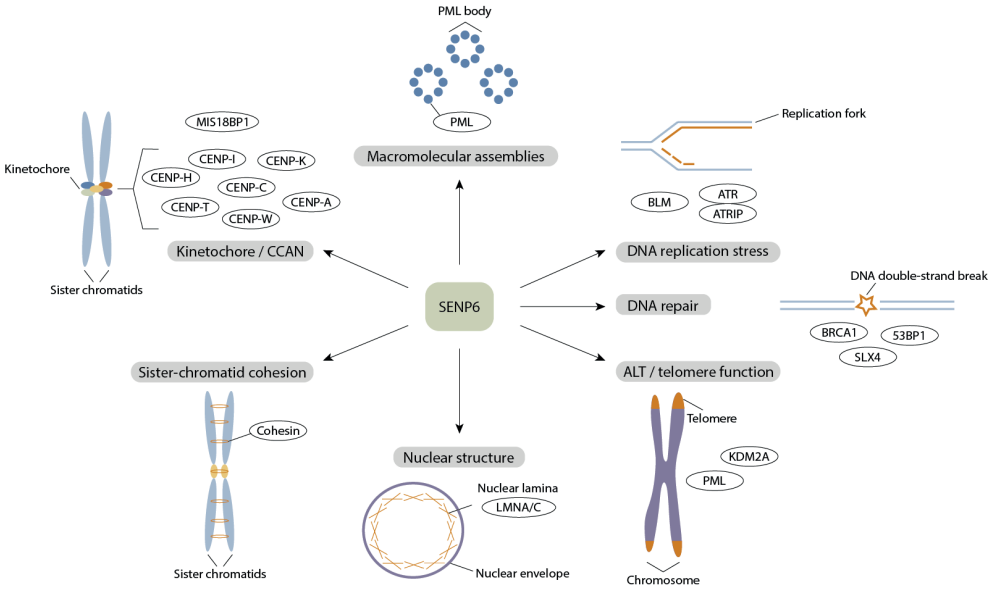

Figure 3. Multifaceted role of sentrin-specific protease 6 (SENP6) in maintaining nuclear integrity. A schematic overview of the diverse functions of SENP6 in maintaining nuclear integrity. The processes regulated by SENP6 are indicated. A selection of proteins that were confirmed to be either directly or indirectly linked to the deconjugation of small ubiquitin-like modifiers (SUMOs) by SENP6 in these processes are highlighted. SENP6 is critical in maintaining genome integrity by playing key roles in processes like DNA replication stress, DNA repair, and alternative lengthening of telomeres (ALT). SENP6 is also pivotal for cell cycle progression by regulating the localisation of constitutive centromere-associated network (CCAN) proteins and CENP-A at the kinetochore, and ensuring the proper cohesion of sister chromatids through the regulation of cohesin. SENP6 is also an important regulator of nuclear lamina integrity and promyelocytic leukemia (PML) body structure and composition (the latter is not discussed in this review). Abbreviations: ATR, ataxia telangiectasia and Rad3-related protein; ATRIP, ATR-interacting protein; BLM, Bloom syndrome protein; CCAN, constitutive centromere-associated network.

INFLAMMATION AND IMMUNITY

SENPs were previously described as being involved in the regulation of NFκB-based inflammatory signalling through deSUMOylation of the kinase NEMO (reviewed in [17]). However, many more roles of SENPs in inflammation and immunity have been unravelled in the past few years. Recent reports have indicated a function of SENPs in innate immunity. Upon viral infection, the retinoic acid-inducible gene-I (RIG-I)– mitochondrial antiviral signalling protein (MAVS) signalling pathway responds to viral RNA, and the **cyclic GMP-AMP synthase–stimulator of interferon genes** (**cGAS–STING) signalling pathway** responds to viral DNA. The RIG-I-MAVS signalling cascade involves the recruitment of the transcription factor IRF3 by the MAVS to stimulate the production of Type 1 interferons. SENP1 was shown to negatively regulate antiviral immunity through this signalling cascade by the

deSUMOylation of MAVS and antagonizing the recruitment and activation of IRF3 [53]. By contrast, SENP7 was previously proposed to potentiate antiviral immunity through the cGAS–STING signalling cascade by the deSUMOylation of cGAS, which promotes its activity and the downstream expression of IRF3-responsive genes [54].

The SENP1–Sirt3 regulatory axis described earlier is also important for metabolic programming and mitochondrial dynamics in immune cells. In the macrophages, the SENP1–Sirt3 signalling pathway controls glutaminolysis in mitochondria, leading to the accumulation of α-ketoglutarate and enhancing the polarisation of M2 macrophages [55]. In T cells, the activation of SENP1–Sirt3 signalling promotes oxidative phosphorylation and mitochondrial fusion, enhancing T cell survival and development of memory [56].

Box 1 | The multifaceted roles of SENP6 in maintaining nuclear integrity

Mechanistically, SENP6 was identified as a key regulator of the chromatin residency of ATR-Chk1 DNA damage checkpoint proteins [15]. In line with this finding, we showed that depletion of SENP6 results in the defective dynamics of SUMO2/3, BRCA1, and 53BP1 at the sites of DNA damage [72]. There are some indications that a novel way in which SENP6 regulates DNA repair proteins is through SUMO2/3 and SIM-mediated formation of transient biomolecular condensates, as the depletion of SENP6 results in the accumulation of selected repair proteins in nuclear condensates [72]. Moreover, SLX4 was identified as a target of SENP6 in proteomic screens [15,22], and was recently shown to regulate the timely assembly and disassembly of SLX4 condensates on chromatin in a SUMO- and SIM-dependent manner, together with RNF4, to locally compartmentalise repair proteins and facilitate repair [73]. In accordance with the vast landscape of the targets of SENP6 identified by mass spectrometry, SENP6 was recently shown to function in even more diverse ways in the context of genome integrity. During replication stress, SENP6 antagonises RNF4-mediated turnover of the Bloom syndrome protein (BLM) helicase at stalled replication forks [74]. Moreover, SENP6 is critical for the alternative lengthening of telomeres (ALT), a mechanism utilised by a subset of cancers, by promoting dissolution of ALT telomeres following recombination-directed telomere synthesis [75]. In maintaining nuclear envelope integrity, SENP6 prevents the hyperSUMOylation of Lamin A/C and the development of laminopathies [76]. Despite the new wealth of knowledge obtained over the past few years regarding the substrates and nuclear functions of SENP6, this is possibly still the tip of the iceberg. In yeast, the SENP6 homolog Ulp2, counteracts SUMO-chain-targeted turnover of structural maintenance of chromosomes (SMC) complexes by the SUMO-targeted ubiquitin ligases (STUbLs) slx5/slx8, which is essential for processes such as sister chromatid cohesion, chromosome condensation, and DNA repair [77]. All the SMC complexes were identified as SENP6 targets in proteomic screens [15,22]. Indeed, the knockdown of SENP6 was confirmed to result in increased SUMOylation of the cohesin subunits SMC1, SMC3, RAD21, and STAG1/2, as well as the cohesin-associated regulatory subunits PDS5A and PDS5B, leading to defective sister chromatid cohesion [15]. While a functional role for SENP6 in regulating condensin (SMC2/SMC4) and the SMC5/6 complex awaits investigation, it is clear that SENP6 plays a multifaceted role in maintaining nuclear integrity.

TUMOUR IMMUNITY

Data from recent years support the role of SENP3 in regulating antitumour immunity. The SENP3–BACH2 deSUMOylation axis controls the function of regulatory T cells, which is reflected by the enhanced tumour immunity upon the depletion of SENP3 [57]. Moreover, activating SENP3 through mutation of its phosphorylation site in tumour cells was shown to supress tumour outgrowth through the infiltration of CD8 T cells and activation of cGAS–STING signalling by the formation of micronuclei [58]. In dendritic cells (DCs), SENP3 is also coupled to the cGAS–STING signalling pathway [59]. DC-derived reactive oxygen species trigger the accumulation of SENP3 and the deSUMOylation of IFI204/IFI16, resulting in activation of the cGAS–STING pathway and enhanced DC antitumour immunity. SENP7 was also shown to sense oxidative stress, in this case, in CD8 T cells, and to sustain their metabolic fitness and anti-tumour effector functions through the deSUMOylation of phosphatase and tensin homolog (PTEN) [60]. The role of SENPs in cancer is discussed in more detail later.

SUMO PROTEASES IN DISEASE

CANCER

Due to the critical roles that SENPs play in regulating progression of the cell cycle and maintaining genomic stability, it comes as no surprise that the dysregulation of SENPs is frequently associated with cancer. Given that this topic has been reviewed extensively previously [61], the scope of our discussion will be confined to summarizing some core concepts, including select illustrative examples. SENPs are generally overexpressed in cancers, although their depletion is also observed in some specific cancer types. SENPs can directly promote tumorigenesis and are commonly linked with unfavourable prognosis and clinical outcomes. Furthermore, there are instances where the expression of SENPs is also correlated with sensitivity and resistance to anticancer drugs.

An example of how the dysregulation of SENPs can directly contribute to tumorigenesis is the stabilisation of the transcription factor c-Myc by SENP1, discussed earlier. C-Myc is one of the most frequently overexpressed proteins in human cancer, and high SENP1 levels correlate with high c-Myc levels in breast cancer tissues [20]. Knockdown of SENP1 was shown to reduce c-Myc levels and supress the proliferation and transformation of cells, illustrating the potential of targeting SENPs in cancer therapy. So far, SENP1–3 have been studied the most, but SENP5–7 are also implicated in several types of cancers. SENP6 is a frequently mutated gene in acute myeloid leukemia (AML) and is significantly overexpressed [62]. By contrast, in lymphomas, SENP6 is frequently deleted and acts as a tumour suppressor through its

pivotal role in maintaining genomic stability [63]. The study also showed that the loss of SENP6 in diffuse B cell lymphomas drives synthetic lethality to poly(ADP-ribose) polymerase (PARP) inhibition, pointing to a potential opportunity for therapeutic intervention.

The SENP-mediated regulation of mitochondrial metabolism can also be linked to tumorigenesis. In prostate cancer cells, SENP1 deSUMOylates hexokinase 2 (HK2), a regulator of glycolysis that couples metabolic reprogramming to cell proliferation in cancer cells [64]. SUMO-defective HK2 preferentially binds to the mitochondria, enhancing the consumption of glucose and the production of lactate, which promotes cancer cell proliferation and resistance to chemotherapy. Indeed, high levels of both SENP1 and HK2 correlated with poor clinical outcomes in prostate cancer patients.

Altogether, it is evident that through the pivotal role of SENPs in the cellular processes that are frequently involved in tumorigenesis, the dysregulation of SENPs plays an important role in many cancers. Gaining a better understanding of which SENPs are dysregulated in different types of cancers, as well as the underlying mechanisms contributing to tumorigenesis and poor clinical outcomes, is essential for providing potential avenues for improving anticancer therapies.

OTHER DISEASES

Several reports from the past few years have suggested the involvement of SENPs in a variety of human diseases beyond cancer. A role of SENPs in cardiovascular health and disease is currently supported by multiple studies, and this has been covered in another review [65]. Moreover, SENP1 was shown to prevent **steatohepatitis** in hepatocyte-specific knockout mice by deSUMOylating RIPK1 and by inhibiting cell death and inflammation [66]. By contrast, liver-specific SENP2 knockout mice were actually more resistant to high-fat-induced steatohepatitis and obesity [67]. Both SENP3 and SENP7 are considered to be important for the assembly and organisation of sarcomeres, and both are targeted in **cachexia** [68,69]. Furthermore, a recent study showed that the inhibition of SENP6 reduced the size of infarcts, neurological deficit scores, and motor and cognitive function in mice after cerebral brain injury, suggesting that targeting SENP6 could serve as a potential therapeutic strategy for mitigating the effects of ischemic stroke [70]. Lastly, in collaboration with others, we recently identified a homozygous stop gain variant of the *SENP7* gene in four infants from the same family that resulted in fatal **arthrogryposis multiplex congenita**, respiratory failure, neutropenia, and early death [71]. This is the first report linking one of the SENPs to Mendelian disease, although some caution is warranted, as this is currently based on only a single family. Due to the therapeutic potential of targeting SENPs in cancer

and other diseases, substantial effort is being put towards the discovery and development of SENP inhibitors (Box 2).

Box 2 | SUMO proteases as therapeutic targets: SENP inhibitors

Because of their therapeutic potential in cancer and other diseases, increasing effort has been put into the discovery and development of SENP inhibitors. The existence of six SENPs, each with isoform-specific characteristics and functions, as well as their differential expression in various cell types, tissues, and diseases, makes them promising candidates for selective targeting of the SUMO system. To date, relatively few inhibitors have been reported, with efforts being primarily focused on SENP1 and SENP2. An in-depth overview of these studies and inhibitors can be found in a recent review [78]. The initial strategies focused on peptide-based inhibitors and were based on electrophilic trapping of the catalytic cysteine residue. However, due to the generally poor pharmacokinetic properties of peptide-based inhibitors, the search for small-molecule inhibitors attracted increasing levels of interest. In recent years, computational approaches, including virtual screening-assisted and molecular docking strategies, have become more important in this pursuit.

Most inhibitors have been identified and validated using in vitro assays. Multiple assays exist to measure the inhibition of SENPs, each with its own advantages and disadvantages [79]. The inhibitory capacity of only a few compounds has been tested in cell lysates or whole cells. For this, good activity-based probes that can be utilised to validate specific and effective inhibition in cells are needed. Moreover, very few compounds have been tested for their effect on cancer cells. Two plant-derived SENP1 inhibitors, triptolide and momordin Ic, suppressed the proliferation of prostate cancer cells in culture and also in vivo in a xenograft mouse model [80,81]. So far, no other SENP inhibitors have been tested in vivo and none has reached (pre) clinical trials.

One of the biggest challenges remaining ahead is the development of isoform-selective inhibitors, due to the high similarity in the catalytic domain, structure, and isopeptidase cleavage chemistry of all the SENPs. In contrast to pan-SENP inhibitors, isoform-specific inhibitors are expected to enable the use of lower effective doses and result in fewer side effects. Currently, another limitation is that most inhibitors identified to date are covalent inhibitors reacting with the cysteine of the active site. Covalent inhibitors are less preferable, as their irreversible nature generally gives a higher risk of unpredictable side effects. More structural information on the SENPs is required for the development of noncovalent inhibitors with targets outside the active site. For SENP3,-5, and-6, no published structural information is available; for SENP1,-2, and-7, only information for their catalytic domains is available.

CONCLUDING REMARKS AND FUTURE PERSPECTIVES

In recent years, more substrates and cellular and physiological processes under the control of SENPs have been revealed. Nevertheless, we are still limited in our knowledge of the range of the substrates regulated by each SENP. The starting point of many studies is a protein of interest regulated by SUMOylation, leading to the identification of the SENP responsible for its deSUMOylation. To obtain a more complete view, future research in the field should

continue to focus on the global identification of SENP substrates through unbiased screening methods under varying physiological conditions, including specific stress conditions and phases of the cell cycle, as well as in different cell types. Currently, experiments looking at SENP function predominantly involve the overexpression or knockdown of the entire protein, which can lead to indirect effects that do not reflect their physiological functions. To address this issue, the field would benefit from SENP inhibitors that are capable of selectively and temporally targeting the catalytic activity of SENPs. No significant advances have been made regarding our knowledge on the SUMO proteases DESI1, DESI2, and USPL1, which are not part of the Ulp/SENP family, since their discovery. We are also still limited in our knowledge on how SENP substrate specificity is determined, and on the spatiotemporal regulation of the different SUMO proteases and their activity (see Outstanding questions).

SENPs have emerged as important players in tumorigenesis and hold promise as viable targets in cancer treatment. Future research should focus on further elucidating which SENPs are dysregulated in different types of cancers, as well as the underlying mechanisms and substrates involved that contribute to tumorigenesis. It will be important to identify the tumours in which SENPs act as oncogenes or tumour suppressors. In this context, SENPs could serve as valuable prognostic markers in a clinical setting. Because of their therapeutic potential in cancer, as well as in various other diseases, increasing effort has been put into the discovery and development of SENP inhibitors. However, this is still in its infancy. One of the biggest challenges remaining ahead is the development of isoform-selective inhibitors, before progressing to (pre)clinical testing and implementation.

Outstanding questions

- Which sets of substrates are regulated by each of the SENPs and in what physiological settings?
- How are the different SENPs and their activity regulated spatiotemporally? How do their N-terminal domains influence their subcellular localisation and substrate specificity? Is there a role for the many phosphorylation sites present in these regions?
- Which SENPs are dysregulated in different types of cancers and various other diseases?
- What are the underlying mechanisms and SENP substrates involved in the development of cancer and other diseases?
- Can SENP inhibitors prove effective in the treatment of cancers and other diseases?

GLOSSARY

APC/C complex: the anaphase-promoting complex is a large multi-subunit E3 ubiquitin ligase that directs cell cycle progression through the degradation of the cell cycle regulatory proteins of the cell cycle.

Arthrogryposis multiplex congenita: a term used to describe a variety of conditions that are characterised by multiple joint contractures (stiffness) and muscle weakness.

Cachexia: a metabolic syndrome characterised by involuntary loss of muscle mass.

cGAS–-STING signalling pathway (cyclic GMP-AMP synthase–stimulator of interferon genes): part of the innate immune system that detects the presence of cytosolic DNA and induces the expression of type I interferons and other inflammatory cytokines.

Chromosome congression: a process by which chromosomes move towards and align at the mitotic spindle equator during the pro-metaphase, forming the metaphase plate.

Constitutive centromere-associated network (CCAN): a group of 16 chromatin-proximal proteins that localise to the centromeres of chromosomes throughout the cell cycle and are essential for the assembly of kinetochores assembly.

Fanconi anaemia ID complex: a protein complex consisting of FANCI and FANCD2, that plays a role in the repair of DNA interstrand crosslinks. Mutations in these proteins lead to Fanconi anaemia, a genetic disease resulting in an impaired response to DNA damage.

Homologous recombination (HR): a pathway of DNA double-strand breakage repair pathway in which undamaged DNA on the sister chromatid or homologous chromosome is used as a template to repair the break, leading to accurate repair.

Kinetochore: a large protein complex that assembles on the centromeres of chromosomes during mitosis to which the microtubules of the mitotic spindle attach to it, thereby promoting proper chromosome segregation.

Mitochondrial fission: a process where one mitochondrion divides into two daughter mitochondria.

Mitophagy: a process that maintains mitochondrial quantity and quality by selectively degrading dysfunctional mitochondria by autophagy.

Non-homologous end-joining: a pathway DNA double-strand breakage repair pathway in which the broken ends of the DNA ends are modified and ligated together without the use of a homologous template, generating deletions or inserts.

PolySUMOylation: small ubiquitin-like modifier (SUMO) 2 and SUMO3 are capable of forming polymeric chains on the target proteins through SUMO modification of the internal lysine residues within SUMO moieties.

Rixosome: a conserved multi-enzyme RNA degradation complex with roles in ribosomal RNA processing, ribosome biogenesis, and gene silencing.

Securin: the substrate of APC/C substrate. During mitosis, it inhibits separase and ensures timely separation of sister chromatids separation.

Segregase p97/VCP: an AAA+ ATPase that extracts ubiquitinated proteins from protein complexes and other cellular structures for proteasomal degradation or substrate recycling.

Spindle assembly: assembly of the mitotic spindle, a microtubule-based structure that attaches to chromosomes and orchestrates their segregation into two daughter cells during cell division.

Steatohepatitis: a liver disease characterised by inflammation and the accumulation of fat in the liver.

SUMO interaction motif (SIM): a short hydrophobic stretch in proteins preceded or succeeded by an acidic region that interacts non-covalently with a conserved surface patch on a SUMO.

SUMO-targeted ubiquitin ligases (STUbLs): a family of SUMO-targeted ubiquitin ligases that recognise polymeric SUMO chains and subsequently ubiquitinate the target protein.

DECLARATION OF INTEREST

The authors have no interests to declare.

REFERENCES

1. Vertegaal, A.C.O. (2022) Signalling mechanisms and cellular functions of SUMO. Nat. Rev. Mol. Cell Biol. 23, 715–731
2. Mukhopadhyay, D. and Dasso, M. (2007) Modification in reverse: the SUMO proteases. Trends Biochem. Sci. 32, 286–295
3. Nayak, A. and Müller, S. (2014) SUMO-specific proteases/ isopeptidases: SENPs and beyond. Genome Biol. 15, 422
4. Hickey, C.M. et al. (2012) Function and regulation of SUMO proteases. Nat. Rev. Mol. Cell Biol. 13, 755–766
5. Owerbach, D. et al. (2005) A proline-90 residue unique to SUMO-4 prevents maturation and sumoylation. Biochem. Biophys. Res. Commun. 337, 517–520
6. Pedrioli, P.G.A. et al. (2006) Automated identification of SUMOylation sites using mass spectrometry and SUMmOn pattern recognition software. Nat. Methods 3, 533–539
7. Matic, I. et al. (2010) Site-specific identification of SUMO-2 targets in cells reveals an inverted SUMOylation motif and a hydrophobic cluster SUMOylation motif. Mol. Cell 39, 641–652
8. Lascorz, J. et al. (2022) SUMO–SIM interactions: from structure to biological functions. Semin. Cell Dev. Biol. 132, 193–202
9. Sriramachandran, A.M. and Dohmen, R.J. (2014) SUMOtargeted ubiquitin ligases. Biochim. Biophys. Acta 1843, 75–85
10. Li, S.-J. and Hochstrasser, M. (1999) A new protease required for cell-cycle progression in yeast. Nature 398, 246–251
11. Li, S.J. and Hochstrasser, M. (2000) The yeast ULP2 (SMT4) gene encodes a novel protease specific for the ubiquitin-like Smt3 protein. Mol. Cell. Biol. 20, 2367–2377
12. Schulz, S. et al. (2012) Ubiquitin-specific protease-like 1 (USPL1) is a SUMO isopeptidase with essential, non-catalytic functions. EMBO Rep. 13, 930–938
13. Shin, E.J. et al. (2012) DeSUMOylating isopeptidase: a second class of SUMO protease. EMBO Rep. 13, 339–346
14. Li, Y. et al. (2022) Structural basis for the SUMO protease activity of the atypical ubiquitin-specific protease USPL1. Nat. Commun. 13, 1819
15. Wagner, K. et al. (2019) The SUMO isopeptidase SENP6 functions as a rheostat of chromatin residency in genome maintenance and chromosome dynamics. Cell Rep. 29, 480–494
16. Lima, C.D. and Reverter, D. (2008) Structure of the human SENP7 catalytic domain and poly-SUMO deconjugation activities for SENP6 and SENP7. J. Biol. Chem. 283, 32045–32055
17. Kunz, K. et al. (2018) SUMO-specific proteases and isopeptidases of the SENP family at a glance. J. Cell Sci. 131, jcs211904
18. Dönig, J. et al. (2023) Characterization of nucleolar SUMO isopeptidases unveils a general p53-independent checkpoint of impaired ribosome biogenesis. Nat. Commun. 14, 8121
19. Kang, X.L. et al. (2010) SUMO-specific protease 2 is essential for suppression of polycomb group protein-mediated gene silencing during embryonic development. Mol. Cell 38, 191–201
20. Sun, X.X. et al. (2018) SUMO protease SENP1 deSUMOylates and stabilizes c-Myc. Proc. Natl Acad. Sci. USA 115, 10983–10988
21. Ryu, H.Y. et al. (2019) The Ulp2 SUMO protease promotes transcription elongation through regulation of histone sumoylation. EMBO J. 38, e102003
22. Liebelt, F. et al. (2019) The poly-SUMO2/3 protease SENP6 enables assembly of the constitutive centromere-associated network by group deSUMOylation. Nat. Commun. 10, 3987
23. Zhou, H.N. et al. (2023) SENP3 and USP7 regulate Polycomb– rixosome interactions and silencing functions. Cell Rep. 42, 112339
24. Roworth, A.P. et al. (2019) Arginine methylation expands the regulatory mechanisms and extends the genomic landscape under E2F control. Sci. Adv. 5, eaaw4640
25. Du, Y.Z. et al. (2018) SUMOylation of the m(6)A-RNA methyltransferase METTL3 modulates its function. Nucleic Acids Res. 46, 5195–5208

26. Bragado, L. et al. (2022) SUMO conjugation regulates the activity of the Integrator complex. Nucleic Acids Res. 50, 12444–12461
27. Zhang, X.D. et al. (2008) SUMO-2/3 modification and binding regulate the association of CENP-E with kinetochores and progression through mitosis. Mol. Cell 29, 729–741
28. Cubeñas-Potts, C. et al. (2013) SENP1 and SENP2 affect spatial and temporal control of sumoylation in mitosis. Mol. Biol. Cell 24, 3483–3495
29. Mukhopadhyay, D. et al. (2010) The SUMO protease SENP6 is essential for inner kinetochore assembly. J. Cell Biol. 188, 681–692
30. Mitra, S. et al. (2020) Genetic screening identifies a SUMO protease dynamically maintaining centromeric chromatin. Nat. Commun. 11, 501
31. Fu, H. et al. (2019) SENP6-mediated M18BP1 deSUMOylation regulates CENP-A centromeric localization. Cell Res. 29, 254–257
32. van den Berg, S.J.W. et al. (2023) p97/VCP drives turnover of SUMOylated centromeric CCAN proteins and CENP-A. Mol. Biol. Cell 34, br6
33. Suhandynata, R.T. et al. (2019) Recruitment of the Ulp2 protease to the inner kinetochore prevents its hyper-sumoylation to ensure accurate chromosome segregation. PLoS Genet. 15, e1008477
34. Quan, Y. et al. (2021) Ctf3/CENP-I provides a docking site for the desumoylase Ulp2 at the kinetochore. J. Cell Biol. 220, e202012149
35. Wei, B. et al. (2018) Mitotic phosphorylation of SENP3 regulates deSUMOylation of chromosome-associated proteins and chromosome stability. Cancer Res. 78, 2171–2178
36. Wang, Y. et al. (2020) P53 suppresses SENP3 phosphorylation to mediate G2 checkpoint. Cell Discov. 6, 21
37. Liu, W. et al. (2023) Lactate regulates cell cycle by remodelling the anaphase promoting complex. Nature 616, 790–797
38. Eifler, K. et al. (2018) SUMO targets the APC/C to regulate transition from metaphase to anaphase. Nat. Commun. 9, 1119
39. Yatskevich, S. et al. (2021) Molecular mechanisms of APC/C release from spindle assembly checkpoint inhibition by APC/C SUMOylation. Cell Rep. 34, 108929
40. Lee, C.C. et al. (2018) Sumoylation promotes optimal APC/C activation and timely anaphase. eLife 7, e29539
41. Galanty, Y. et al. (2009) Mammalian SUMO E3-ligases PIAS1 and PIAS4 promote responses to DNA double-strand breaks. Nature 462, 935–939
42. Garvin, A.J. and Morris, J.R. (2017) SUMO, a small, but powerful, regulator of double-strand break repair. Philos. Trans. R. Soc. Lond. Ser. B Biol. Sci. 372, 20160281
43. Garvin, A.J. et al. (2013) The deSUMOylase SENP7 promotes chromatin relaxation for homologous recombination DNA repair. EMBO Rep. 14, 975–983
44. Zhang, T. et al. (2022) Crosstalk between SUMOylation and ubiquitylation controls DNA end resection by maintaining MRE11 homeostasis on chromatin. Nat. Commun. 13, 5133
45. Garvin, A.J. et al. (2019) The deSUMOylase SENP2 coordinates homologous recombination and nonhomologous end joining by independent mechanisms. Genes Dev. 33, 333–347
46. Bologna, S. et al. (2015) Sumoylation regulates EXO1 stability and processing of DNA damage. Cell Cycle 14, 2439–2450
47. Dou, H. et al. (2010) Regulation of DNA repair through deSUMOylation and SUMOylation of replication protein A complex. Mol. Cell 39, 333–345
48. Gibbs-Seymour, I. et al. (2015) Ubiquitin-SUMO circuitry controls activated Fanconi anemia ID complex dosage in response to DNA damage. Mol. Cell 57, 150–164
49. Zunino, R. et al. (2009) Translocation of SenP5 from the nucleoli to the mitochondria modulates DRP1-dependent fission during mitosis. J. Biol. Chem. 284, 17783–17795
50. Waters, E. et al. (2022) The SUMO protease SENP3 regulates mitochondrial autophagy mediated by Fis1. EMBO Rep. 23, e48754
51. Wang, T.S. et al. (2019) SENP1–Sirt3 signaling controls mitochondrial protein acetylation and metabolism. Mol. Cell 75, 823–834

52. Liu, Y. et al. (2023) Mitochondrial SENP2 regulates the assembly of SDH complex under metabolic stress. Cell Rep. 42, 112041
53. Dai, T. et al. (2023) MAVS deSUMOylation by SENP1 inhibits its aggregation and antagonizes IRF3 activation. Nat. Struct. Mol. Biol. 30, 785–799
54. Cui, Y. et al. (2017) SENP7 Potentiates cGAS activation by relieving SUMO-mediated inhibition of cytosolic DNA sensing. PLoS Path. 13, e1006156
55. Zhou, W. et al. (2022) SENP1–Sirt3 signaling promotes alphaketoglutarate production during M2 macrophage polarization. Cell Rep. 39, 19
56. He, J.L. et al. (2021) Glucose limitation activates AMPK coupled SENP1–Sirt3 signalling in mitochondria for T cell memory development. Nat. Commun. 12, 14
57. Yu, X.Y. et al. (2018) SENP3 maintains the stability and function of regulatory T cells via BACH2 deSUMOylation. Nat. Commun. 9, 3157
58. Hu, G. et al. (2022) Mitotic SENP3 activation couples with cGAS signaling in tumor cells to stimulate anti-tumor immunity. Cell Death Dis. 13, 640
59. Hu, Z. et al. (2021) SENP3 senses oxidative stress to facilitate STING-dependent dendritic cell antitumor function. Mol. Cell 81, 940–952.e5
60. Wu, Z. et al. (2022) SENP7 senses oxidative stress to sustain metabolic fitness and antitumor functions of CD8+ T cells. J. Clin. Invest. 132, e155224
61. Lara-Ureña, N. et al. (2022) Cancer-associated dysregulation of Sumo regulators: proteases and ligases. Int. J. Mol. Sci. 23, 8012
62. Shi, L. et al. (2020) Analyzing the key gene expression and prognostics values for acute myeloid leukemia. Transl. Cancer Res. 9, 7284–7298
63. Schick, M. et al. (2022) Genetic alterations of the SUMO isopeptidase SENP6 drive lymphomagenesis and genetic instability in diffuse large B-cell lymphoma. Nat. Commun. 13, 281
64. Xun, S.G. et al. (2021) SUMOylation controls the binding of hexokinase 2 to mitochondria and protects against prostate cancer tumorigenesis. Nat. Commun. 12, 14
65. Hotz, P.W. et al. (2021) SUMO-specific isopeptidases tuning cardiac SUMOylation in health and disease. Front. Mol. Biosci. 8, 786136
66. Yan, L.J. et al. (2022) SENP1 prevents steatohepatitis by suppressing RIPK1-driven apoptosis and inflammation. Nat. Commun. 13, 19
67. Liu, Y. et al. (2021) Hepatic small ubiquitin-related modifier (SUMO)–specific protease 2 controls systemic metabolism through SUMOylation-dependent regulation of liver–adipose tissue crosstalk. Hepatology 74, 1864–1883
68. Amrute-Nayak, M. et al. (2022) SENP7 deSUMOylase-governed transcriptional program coordinates sarcomere assembly and is targeted in muscle atrophy. Cell Rep. 41, 111702
69. Nayak, A. et al. (2019) Regulation of SETD7 methyltransferase by SENP3 is crucial for sarcomere organization and cachexia. Cell Rep. 27, 2725–2736.e4
70. Mao, M. et al. (2022) SENP6 induces microglial polarization and neuroinflammation through de-SUMOylation of Annexin-A1 after cerebral ischaemia–reperfusion injury. Cell Biosci. 12, 113
71. Samra, N. et al. (2023) Exome sequencing links the SUMO protease SENP7 with fatal arthrogryposis multiplex congenita, early respiratory failure and neutropenia. J. Med. Genet. 60, 1133–1141
72. Claessens, L.A. et al. (2023) SENP6 regulates localization and nuclear condensation of DNA damage response proteins by group deSUMOylation. Nat. Commun. 14, 5893
73. Alghoul, E. et al. (2023) Compartmentalization of the SUMO/ RNF4 pathway by SLX4 drives DNA repair. Mol. Cell 83, 1640–1658.e9
74. Ellis, N. et al. (2021) RNF4 regulates the BLM helicase in recovery from replication fork collapse. Front. Genet. 12, 753535
75. Li, F. et al. (2023) Histone demethylase KDM2A is a selective vulnerability of cancers relying on alternative telomere maintenance. Nat. Commun. 14, 1756
76. Liczmanska, M. et al. (2023) SUMO protease SENP6 protects the nucleus from hyperSUMOylation-induced laminopathy-like alterations. Cell Rep. 42, 112960
77. Psakhye, I. and Branzei, D. (2021) SMC complexes are guarded by the SUMO protease Ulp2 against SUMO-chain-mediated turnover. Cell Rep. 36, 109485

78. Tokarz, P. and Woźniak, K. (2021) SENP proteases as potential targets for cancer therapy. Cancers 13, 2059
79. Jia, Y. et al. (2019) Chemical tools and biochemical assays for SUMO specific proteases (SENPs). ACS Chem. Biol. 14, 2389–2395
80. Huang, W. et al. (2012) Triptolide inhibits the proliferation of prostate cancer cells and down-regulates SUMO-specific protease 1 expression. PLoS One 7, e37693
81. Wu, J. et al. (2016) Momordin Ic, a new natural SENP1 inhibitor, inhibits prostate cancer cell proliferation. Oncotarget 7, 58995–59005
82. Cheng, J. et al. (2007) SUMO-specific protease 1 is essential for stabilization of HIF1alpha during hypoxia. Cell 131, 584–595
83. Lao, Y. et al. (2018) DeSUMOylation of MKK7 kinase by the SUMO2/3 protease SENP3 potentiates lipopolysaccharide-induced inflammatory signaling in macrophages. Biol. Chem. 293, 3965–3980
84. Li, J. et al. (2018) Desumoylase SENP6 maintains osteochondroprogenitor homeostasis by suppressing the p53 pathway. Nat. Commun. 9, 143
85. Huang, C.-J. et al. (2017) Maternal SENP7 programs meiosis architecture and embryo survival in mouse. Biochim. Biophys. Acta. Mol. Cell. Res. 1864, 1195–1206