Cell Insight 2 (2023) 100128

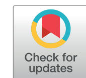
Contents lists available at ScienceDirect

Cell Insight

journal homepage: www.journals.elsevier.com/cell-insight

Review

Preserving genome integrity: The vital role of SUMO-targeted ubiquitin ligases



Jinhua Han [a,b,1,**], Yanhua Mu [c,1], Jun Huang [a,b,*]

[a] Institute of Geriatrics, Affiliated Zhejiang Hospital, Zhejiang University School of Medicine, Hangzhou, 310030, Zhejiang, China

[b] The MOE Key Laboratory of Biosystems Homeostasis & Protection and Innovation Center for Cell Signaling Network, Life Sciences Institute, Zhejiang University, Hangzhou, 310058, Zhejiang, China

[c] National-Local Joint Engineering Research Center of Biodiagnosis & Biotherapy, The Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, 710004, Shaanxi, China

ARTICLE INFO

Keywords:
STUbLs
RNF4
RNF111
Genome integrity

ABSTRACT

Various post-translational modifications (PTMs) collaboratively fine-tune protein activities. SUMO-targeted ubiquitin E3 ligases (STUbLs) emerge as specialized enzymes that recognize SUMO-modified substrates through SUMO-interaction motifs and subsequently ubiquitinate them via the RING domain, thereby bridging the SUMO and ubiquitin signaling pathways. STUbLs participate in a wide array of molecular processes, including cell cycle regulation, DNA repair, replication, and mitosis, operating under both normal conditions and in response to challenges such as genotoxic stress. Their ability to catalyze various types of ubiquitin chains results in diverse proteolytic and non-proteolytic outcomes for target substrates. Importantly, STUbLs are strategically positioned in close proximity to SUMO proteases and deubiquitinases (DUBs), ensuring precise and dynamic control over their target proteins. In this review, we provide insights into the unique properties and indispensable roles of STUbLs, with a particular emphasis on their significance in preserving genome integrity in humans.

1. Introduction

Genome integrity serves as the foundation for maintaining cellular homeostasis, making it crucial for preventing carcinogenesis and age-related diseases (Hanahan, 2022; Hanahan & Weinberg, 2011). The preservation of genome stability relies on the precise orchestration of multiple intricate processes, including accurate DNA replication, effective DNA damage response, and appropriate chromosome segregation, among a plethora of other essential processes (Bakhoum, Thompson, Manning, & Compton, 2009; Ciccia & Elledge, 2010; Jackson & Bartek, 2009; Jeggo, Pearl, & Carr, 2016; Lombard et al., 2005; MacNeill, 2005; Rickman & Smogorzewska, 2019). These orchestrated pathways work together to ensure the faithful duplication and transmission of genetic information stored in DNA.

Post-translational modifications (PTMs) involve covalent attachments of small modifiers to proteins, rapidly and reversibly regulating protein functions (Lee, Hammaren, Savitski, & Baek, 2023; Millan-Zambrano, Burton, Bannister, & Schneider, 2022). Among these known protein modifiers, ubiquitin (Ub) and its relative, small ubiquitin-related modifier (SUMO), play key roles in various genome maintenance pathways (Bergink & Jentsch, 2009; Gatel, Piechaczyk, & Bossis, 2020; Jansen & Vertegaal, 2021). Interestingly, a family of proteins known as SUMO-targeted ubiquitin ligases (STUbLs) has been identified to facilitate crosstalk between the SUMO and Ub systems through SUMO-interaction motifs (SIMs). STUbLs are unique E3 ubiquitin ligases that control the abundance and subcellular localization of SUMOylated proteins (Perry, Tainer, & Boddy, 2008). Given the integral roles of ubiquitination and SUMOylation in maintaining genomic integrity, the absence of STUbLs results in genomic instability and heightened sensitivity to genotoxic stress (Chang, Oram, & Bielinsky, 2021; Jalal, Chalissery, & Hassan, 2017; Munk et al., 2017; Xiao et al., 2015).

2. A brief overview of the ubiquitin and SUMO modification systems

Reversible modification of proteins by Ub or SUMO plays a regulatory

* Corresponding author. Institute of Geriatrics, Affiliated Zhejiang Hospital, Zhejiang University School of Medicine, Hangzhou, 310030, Zhejiang, China.
** Corresponding author. Institute of Geriatrics, Affiliated Zhejiang Hospital, Zhejiang University School of Medicine, Hangzhou, 310030, Zhejiang, China.
E-mail addresses: jhhan2011@zju.edu.cn (J. Han), jhuang@zju.edu.cn (J. Huang).
[1] These authors contributed equally to this work.

https://doi.org/10.1016/j.cellin.2023.100128
Received 3 October 2023; Received in revised form 9 October 2023; Accepted 9 October 2023
Available online 23 October 2023
2772-8927/© 2023 The Authors. Published by Elsevier B.V. on behalf of Wuhan University. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

role in most aspects of eukaryotic cellular processes (Bergink & Jentsch, 2009). The process of ubiquitin modification, known as ubiquitination, occurs through a sequential cascade involving the E1 Ub-activating enzyme, the E2 Ub-conjugating enzyme, and the E3 Ub-protein ligase (Maspero & Polo, 2016). Initially, E1 activates mature Ub in an adenosine triphosphate (ATP)-dependent manner and transfers it to E2, forming a thioester bond between the active cysteine of E2 and the C-terminal carboxyl group of Ub. The final step of Ub transfer is catalyzed by the E3 Ub ligase, which simultaneously interacts with a Ub-loaded E2 enzyme and a specific substrate, facilitating the covalent linkage between the lysine ε-amino group of the substrate and the C-terminal glycine residue of Ub (Dove et al., 2017; Maspero & Polo, 2016; Pao et al., 2018; Streich & Lima, 2016). Subsequent ubiquitination events may occur on the same substrate, either at additional sites (multi-monoubiquitination) or by forming distinct Ub polymers (polyubiquitination). Ub itself contains seven internal lysine residues (K6, K11, K27, K29, K33, K48, K63) and an N-terminal methionine (M1) that can be attached to another Ub moiety, resulting in distinct Ub chains serving as different signals (Branigan, Plechanovova, Jaffray, Naismith, & Hay, 2015; Bremm, Freund, & Komander, 2010; Saeki, 2017). The ubiquitin codes typically regulate protein stability by providing proteasomal targeting signals or modulate protein interactions and activities. For instance, K48-linked polyubiquitin chains typically target proteins for degradation, whereas monoubiquitination or K63-linked chains serve as signals in various cellular processes, such as DNA repair (Castaneda et al., 2016; Jung et al., 2013). The specificity of Ub linkage types and substrates is substantially determined by E2-E3 pairs, given that there are only 2 E1s, but approximately 40 E2s and over 600 E3s in humans (Kim et al., 2007; Scott et al., 2016; Wang & Pickart, 2005). The reversible nature of ubiquitination is facilitated by Ub-specific proteases known as deubiquitinases, or DUBs (Chen, 2016; David, 2011).

Despite sharing only 18% sequence identity, SUMO is structurally related to Ub because they both adopt the β-grasp fold (Johnson, 2004). Similar to ubiquitination, SUMOylation involves a three-step cascade that includes a single dimeric E1 enzyme (SAE1/UBA2), a unique E2 enzyme (UBC9), and a limited number of E3 ligases (Okuma, Honda, Ichikawa, Tsumagari, & Yasuda, 1999; Wang et al., 2007; Wang et al., 2010). SUMOylation typically occurs on a specific lysine residue within the consensus motif ψ-K-X-E/D (where ψ represents a large hydrophobic amino acid, and X can be any amino acid). This motif is directly recognized by the E2 enzyme, UBC9 (Hoege, Pfander, Moldovan, Pyrowolakis, & Jentsch, 2002; Jansen & Vertegaal, 2021). SUMO E3 ligases appear to contribute to substrate specificity and conjugation efficiency by binding both the SUMO-loaded E2 enzyme and the substrate, facilitating the covalent linkage between the lysine residue of the specific substrate and the C-terminal glycine residue of SUMO (Gill, 2004; Joazeiro & Weissman, 2000).

While yeast contain only one SUMO protein, vertebrates have at least three SUMO isoforms, namely SUMO1-3. Mature SUMO2 and SUMO3 are collectively referred to as SUMO2/3 because they share 97% sequence identity with each other but have only about 50% overlap with mature SUMO1 (Bergink & Jentsch, 2009; Bouchard et al., 2021; Jansen & Vertegaal, 2021; Johnson, 2004). SUMO2/3 possess an N-terminal ψ-K-X-E consensus motif and efficiently form SUMO chains, a property that SUMO1 lacks (Yang, Hsu, Ting, Liu, & Hwang, 2006). SUMOs are predominantly distributed in the nucleus. Among the SUMO isoforms, SUMO2 is the most abundant member and can compensate for the absence of SUMO1 and SUMO3, making it essential for embryonic development in mammals (Wang et al., 2014). The removal of SUMO moieties from substrates is catalyzed by a family of cysteine proteases known as SUMO-specific proteases (SENPs), which are also responsible for maturing precursor SUMO molecules by exposing their C-terminal di-Glycine motif required for conjugation (Hay, 2007; Hickey, Wilson, & Hochstrasser, 2012; Mukhopadhyay & Dasso, 2007).

3. SUMO-targeted ubiquitin ligases

SUMO-targeted ubiquitin ligases (STUbLs) are RING-type E3 ubiquitin ligases that specifically prime SUMOylated proteins for ubiquitination, thereby regulating protein turnover and cellular responses (Y. C. Chang et al., 2021; Perry et al., 2008). STUbLs recognize SUMOylated proteins through conserved SUMO-interaction motifs (SIMs), typically composed of short stretches containing large hydrophobic residues such as leucine (L), isoleucine (I), or valine (V), flanked by acidic residues that enhance affinity for SUMO via electrostatic interactions (Boutell et al., 2011; Perry et al., 2008; Prudden et al., 2007; Xu et al., 2014).

As of now, the identification of STUbLs remains limited, with only a small number having been characterized (Fig. 1). *Saccharomyces cerevisiae* possesses three STUbLs: Uls1, the heterodimeric Slx5-Slx8 (Uls2), and Rad18 (Parker & Ulrich, 2012; Uzunova et al., 2007; Xie et al., 2007). While Rad18 preferentially ubiquitinates SUMOylated PCNA to initiate DNA damage bypass, Uls1 and Slx5-Slx8 mediate the degradation of polySUMOylated proteins by the proteasome. Mutations in Uls1 or Slx5-Slx8 result in the accumulation of SUMOylated proteins. Dysfunction of the Rfp1/Rfp2-Slx8 heterodimer in *Schizosaccharomyces pombe* leads to a similar accumulation of SUMOylated proteins (Prudden et al., 2007; Sun, Leverson, & Hunter, 2007). Intriguingly, this phenotype can be complemented by the expression of *Homo sapiens* RNF4, indicating that STUbLs are functionally conserved from yeast to humans. In *Drosophila melanogaster*, Degringolade (Dgrn), and in *Homo sapiens*, RNF111 (also known as Arkadia), also function as STUbLs (Abed et al., 2011; Erker et al., 2013; Poulsen et al., 2013).

Through their precise regulation of SUMOylated proteins, STUbLs contribute to maintaining protein quality control and genome stability. Dysfunction of STUbLs has been implicated in cancer, neurodegenerative disorders, and other diseases. In this review, we discuss the importance of human STUbLs, RNF4 and RNF111, in maintaining genome integrity (Fig. 2 and Table 1).

4. RNF4 and its diverse role in genome maintenance

Mammalian RNF4 is an orthologue of fission yeast Rfp1/Rfp2 and specifically targets SUMOylated proteins for ubiquitination in a SIM-dependent manner (Jansen & Vertegaal, 2021; Keusekotten et al., 2014; Kosoy, Calonge, Outwin, & O'Connell, 2007; Prudden et al., 2007; Sun et al., 2007; Wilson, 2017). Human RNF4 is a protein consisting of 190 amino acids, characterized by four N-terminal tandem SIMs and a C-terminal canonical C3HC4 RING-finger domain (Chiariotti et al., 1998; Hu et al., 2010; Moilanen et al., 1998). Adjacent to the SIMs (residues 36–70), there exists a highly conserved arginine-rich motif (ARM, residues 73–82), which enhances RNF4's specificity for substrates that are both SUMOylated and phosphorylated (Kuo et al., 2014; Sun et al., 2007; Tatham et al., 2008). This specificity is derived from the interaction of the positively charged ARM with phosphorylated substrates. Additionally, the ARM promotes the interaction between the SIMs and the RING domain of RNF4, thereby facilitating the E3 ligase activity of RNF4 (Kuo et al., 2014; Tatham et al., 2008). Moreover, RNF4 contains three basic RKK residues (residues 177–179) bordering the RING domain (residues 132–177), enabling RNF4 to bind DNA and nucleosomes (Groocock et al., 2014). In vivo, RNF4 is predominantly monomeric and inactive. However, once polySUMO chains become available, RNF4 is activated through RING domain mediated dimerization (Branigan et al., 2015; Liew, Sun, Hunter, & Day, 2010; Plechanovova et al., 2011; Rojas-Fernandez et al., 2014). Considering the crucial roles of ubiquitination and SUMOylation in maintaining genomic integrity, the STUbL RNF4 plays diverse roles in protecting against genome instability throughout the cell cycle (Chang et al., 2021; Sun et al., 2007; Wagner et al., 2019). In the following sections, we will discuss the major contributions of RNF4 in regulating promyelocytic leukemia (PML) homeostasis, DNA repair, DNA replication, and mitosis.

A

Species	STUbL	Length	SIM domain	E3 ligase activity of the RING domain
S. cerevisiae	Uls1	1619 aa	4	Ub E3 ligase
	Uls2 Slx5	619 aa	5	Ub E3 ligase
	Uls2 Slx8	274 aa	1	
	Rad18	487 aa	1	Ub E3 ligase
S. pombe	Rfp1/Rfp2	254 aa/205 aa	2	-
	Slx8	269 aa	1	Ub E3 ligase
D. melanogaster	Dgrn	319 aa	2	Ub E3 ligase
H. Sapiens	RNF4	190 aa	4	Ub E3 ligase
	RNF111	994 aa	3	Ub, NEDD8 E3 ligase

B

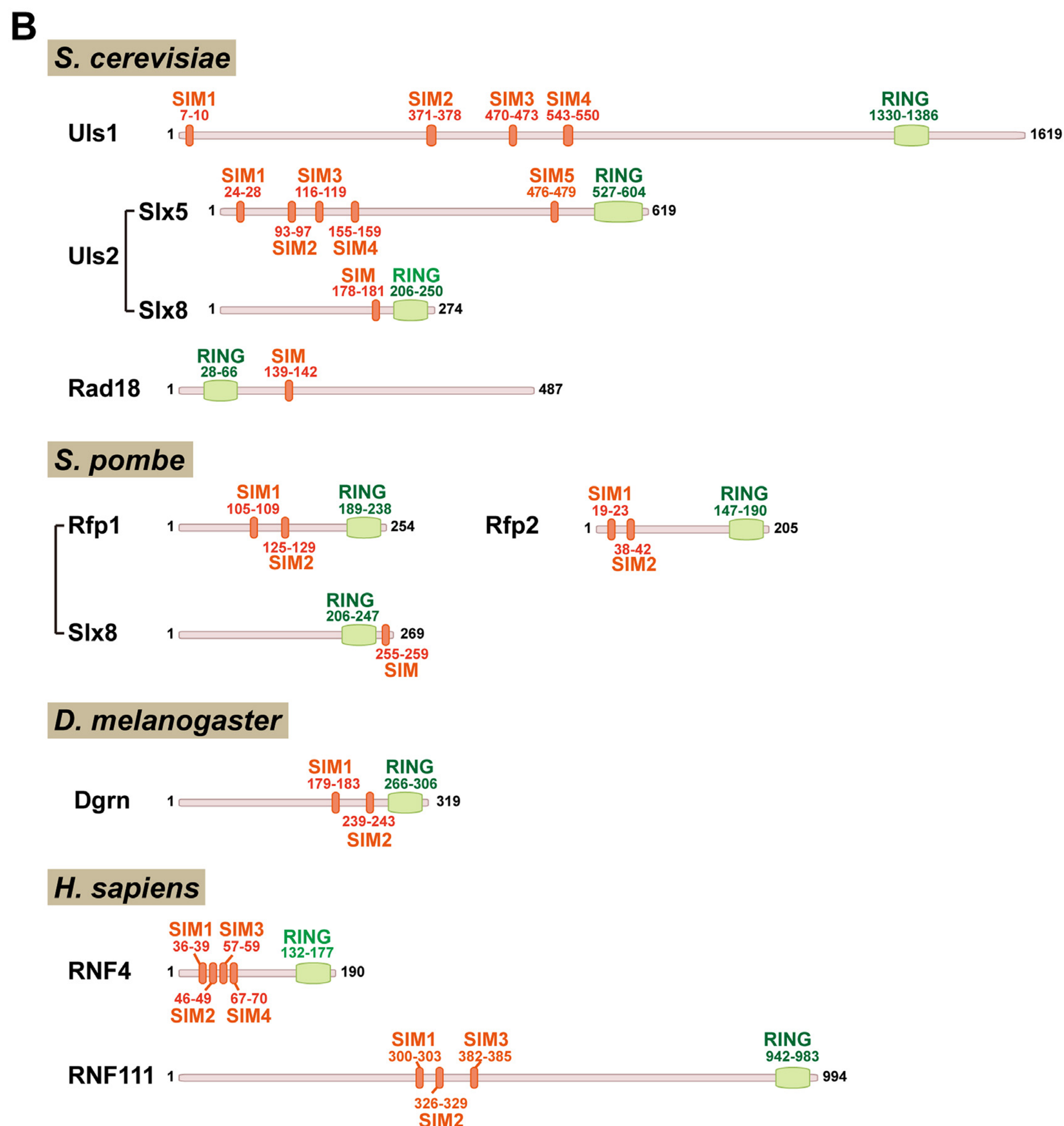


Fig. 1. STUbL domain structures. (a) An overview of STUbLs in various organisms. *Saccharomyces cerevisiae* possesses three STUbLs: Uls1, the heterodimer Slx5-Slx8 (Uls2), and Rad18. In *Saccharomyces pombe*, Slx8 interacts exclusively with either Rfp1 or Rfp2 to form a functional heterodimeric STUbL. In *Drosophila melanogaster*, it is Degringolade (Dgrn), while in *Homo sapiens*, it's RNF4 and RNF111/Arkadia. (b) Schematic representations of the domain structures of STUbL proteins. The domain information was sourced from Uniprot (https://www.uniprot.org/) and GPS-SUMO (https://sumo.biocuckoo.cn/userguide.php). The orange bar represents the SUMO-interacting motif (SIM), and the green bar represents the RING (really interesting new gene) domain. Abbreviations: SIM, SUMO-interacting motif; RING, really interesting new gene; aa, amino acids.

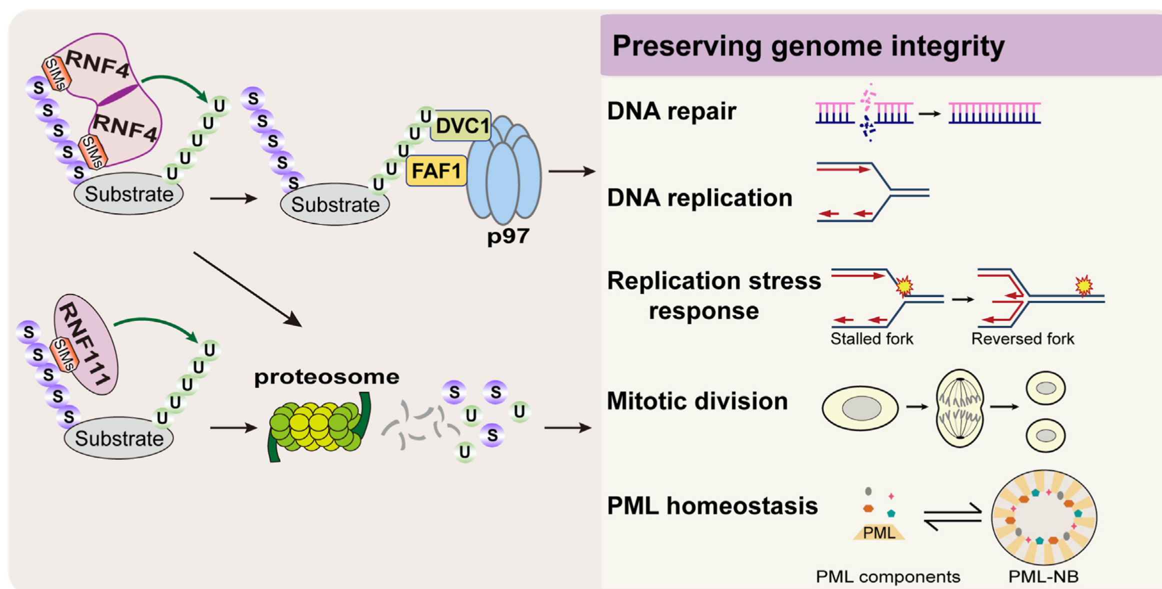


Fig. 2. The Crucial Role of Human STUbLs, RNF4, and RNF111, in Maintaining Genome Integrity. Human RNF4 and RNF111 recognize SUMOylated proteins through their conserved SIM domains and attach polyubiquitin chains to SUMOylated substrates via the RING domain. Upon binding to polySUMOylated substrates, RNF4 undergoes activation through dimerization. RNF4 and RNF111 either mediate the proteolytic degradation of their targets or facilitate substrate extraction by the ATPase p97 with its cofactors DVC1 or FAF1. Consequently, STUbLs play diverse roles in DNA repair, DNA replication, replication stress response, mitotic division, and PML homeostasis, underscoring their significance in maintaining genome integrity. S, SUMO; U, Ub.

Table 1
Substrates of human STUbL proteins.

STUbLs	Substrates	Functions in preserving genome integrity
RNF4	PML/PML-fusion protein, SP100, TDG, HIPK2	PML homeostasis
	MDC1, CtIP, KAP1, 53BP1, BRCA1, BARD1, RPA1, ATRIP, FANCI, FANCD2, FANCA, TOP-DPCs, trapped PARP1	DNA repair
	TOP2A	Replication stress response
	CENPI, Mis18BP1, CENP-B	Mitotic division
RNF111	PML	PML homeostasis
	XPC, Pol η	DNA repair

4.1. Regulation of PML homeostasis

Dynamic super-assembled PML nuclear bodies (PML-NBs) are discrete, membraneless macromolecular organelles tightly attached to the nuclear matrix. PML-NBs modulate a broad range of biological processes, including protein modifications, DNA repair, and transcriptional regulation (Chang et al., 2018; Corpet et al., 2020). Therefore, maintaining PML homeostasis is vital for genome stability. PML, the core component of PML-NBs, was identified as the first in vivo target of human RNF4 to undergo SUMO-triggered K48-linked polyubiquitination for further degradation (Lallemand-Breitenbach et al., 2008; Tatham et al., 2008). The arginine methyltransferase PRMT5 methylates RNF4 at Arg164 to block the interaction between RNF4 and the PML fusion protein PML-RARα, preserving the protein stability of PML-RARα (Huang et al., 2022). In addition to PML/PML-fusion protein, RNF4 is characterized by regulating PML homeostasis through the degradation of several other resident components of PML-NBs, such as homeodomain-interacting protein kinase 2 (HIPK2), thymine DNA glycosylase (TDG), and SP100 (Moriyama et al., 2014; Sahin et al., 2014).

Beyond directly modulating the degradation of PML-NBs components, RNF4 has been found to play new roles in biological processes involving PML-NBs. By generating SUMO-dependent ubiquitin chains, RNF4 promotes the recruitment of RNF168 and the downstream PML-NBs to DNA lesions under genotoxic stress (Shire et al., 2016; Vancurova et al., 2019). Failure to clear misfolded or aggregated proteins often leads to neurodegenerative diseases, such as Alzheimer's and Parkinson's (Peng, Trojanowski, & Lee, 2020; Ross & Poirier, 2004). In response to proteotoxic stress, misfolded proteins or aggregation-prone RNA binding proteins (RPBs) are recognized and SUMOylated by PML or other SUMO E3 ligases (Guo et al., 2014; Keiten-Schmitz et al., 2020). RNF4 then facilitates the proteasomal degradation of SUMO-labeled misfolded proteins by attaching K48-linked polyubiquitin signals. This RNF4-dependent protein quality surveillance pathway may open up new perspectives in understanding the pathogenesis and clinical therapy of neurodegenerative diseases.

4.2. Regulation of DNA repair

Our genomic integrity faces constant challenges from both exogenous and endogenous toxins, leading to various forms of DNA damage. Cells have developed a surveillance mechanism known as the DNA damage response (DDR) to address these DNA lesions (Ciccia & Elledge, 2010; Jackson & Bartek, 2009; Pilie, Tang, Mills, & Yap, 2019). Defects in DDR can result in genomic instability, potentially leading to senescence or cancer (Jackson & Bartek, 2009; Schumacher, Pothof, Vijg, & Hoeijmakers, 2021). Among the various forms of DNA damage, DNA double-strand breaks (DSBs) are particularly detrimental as they disrupt the physical continuity of chromosomes (Canela et al., 2017; Katsuki, Jeggo, Uchihara, Takata, & Shibata, 2020). Cells utilize two major pathways, non-homologous end joining (NHEJ) and homologous recombination (HR), to repair DSBs (Katsuki et al., 2020). NHEJ operates throughout interphase and repairs DSBs by rejoining the broken ends with simple end trimming. This high-efficiency repair mechanism safeguards genome integrity but may compromise fidelity. In contrast to NHEJ, HR primarily occurs during the late S and G2 phases of the cell cycle, when sister chromatids are accessible as repair templates (Zhang & Gong, 2021).

RNF4 is swiftly recruited to DNA damage sites, playing a crucial role in promoting the repair of DSBs. It recognizes DNA damage-induced SUMOylation, mediated by SUMO E3 ligases PIAS1 and PIAS4, through its tandem SIMs (Galanty, Belotserkovskaya, Coates, & Jackson, 2012;

Vyas et al., 2013; Yin et al., 2012). RNF4 then catalyzes and amplifies ubiquitination around the damaged areas. Several components of the DDR undergo SUMOylation in response to DNA damage and are targeted by RNF4 for subsequent degradation, facilitating efficient DSB repair through NHEJ or HR.

One such target of RNF4 is Mediator of DNA Damage Checkpoint 1 (MDC1). Upon DSB induction, MDC1 becomes SUMOylated at Lys1840 (Galanty et al., 2012; Luo, Zhang, Wang, Yuan, & Lou, 2012; Vyas et al., 2013; Yin et al., 2012). Subsequently, RNF4 is recruited to DSB sites by recognizing SUMOylated MDC1 and catalyzes polyubiquitination of MDC1, leading to its timely removal (Luo et al., 2012; Vyas et al., 2013). Consequently, RNF4 integrates SUMO modification and ubiquitin signaling into the cellular response to genotoxic stress.

Recent discoveries have revealed that the removal of MDC1 by RNF4 is tightly regulated by two enzymes: the deubiquitinase ataxin-3 and the SUMO protease SENP2 (Garvin et al., 2019; Pfeiffer et al., 2017). Ataxin-3, a member of the Josephin protease family, is recruited to DSBs through DNA damage-induced SUMOylation. As a SUMO-activated deubiquitinase, ataxin-3 prevents the premature removal of MDC1 from DSBs by counteracting RNF4-mediated ubiquitination of MDC1, thereby facilitating the initiation of the DDR and DNA repair (Pfeiffer et al., 2017). Additionally, the SUMO protease SENP2 has been found to protect MDC1 from inappropriate SUMOylation. However, this protective mechanism is impaired by DNA damage, allowing MDC1 to undergo SUMOylation and subsequent ubiquitination by RNF4 (Garvin et al., 2019). This timely regulation is essential for maintaining an adequate supply of SUMO and is critical for DSB repair. In summary, the precise temporal and spatial control of MDC1 turnover is a prerequisite for appropriate DSB repair.

During the S phase of the cell cycle, RNF4 undergoes phosphorylation by CDK2 at T26 and T112. This phosphorylation event enhances the E3 ubiquitin ligase activity of RNF4, which, in turn, accelerates the degradation of MDC1 (Luo et al., 2015). This process is essential to ensure the proper repair of DNA through HR.

HR repair initiation is dependent on DNA end resection (Cejka & Symington, 2021; Symington & Gautier, 2011). The master kinase ATM plays a crucial role by orchestrating a sequence of posttranslational modifications on the key resection factor CtIP (Chapman, Taylor, & Boulton, 2012; Jasin & Rothstein, 2013; Symington & Gautier, 2011). These modifications precisely control the extent of DNA end resection. In response to DSB induction, CtIP undergoes hyperphosphorylation by ATM (H. Wang et al., 2013). Subsequently, PIAS4 exhibits a preference for the hyperphosphorylated form of CtIP and transfers SUMO chains to CtIP's lysine 578 (Han et al., 2021; Locke et al., 2021). This SUMO-modified and hyperphosphorylated CtIP is then recognized and catalyzed by RNF4 for further turnover (Han et al., 2021). This regulatory step limits excessive resection of DNA ends, ensuring that HR proceeds appropriately without overresection. In this way, the phosphorylation and SUMOylation of CtIP, followed by its controlled turnover by RNF4, collectively contribute to the precise regulation of DNA end resection during HR repair.

In addition, various other factors involved in DSB repair, including Kruppel-associated box (KRAB)-associated protein 1 (KAP1), BRCA1, BARD1, 53BP1, RPA1, and ATRIP have been identified as direct substrates of RNF4 (Galanty et al., 2012; Guzzo et al., 2012; Kumar, Gonzalez-Prieto, Xiao, Verlaan-de Vries, & Vertegaal, 2017; Kuo et al., 2014; Pfeiffer et al., 2017; Vyas et al., 2013; Yin et al., 2012). RNF4 regulates their proteasome-mediated turnover at DNA damage sites. Consequently, the deficiency of RNF4 impairs DSB repair and checkpoint activation, rendering cells hypersensitive to DNA-damaging agents (Chang et al., 2018; Maure, Moser, Jaffray, A, & Hay, 2016; Ragland et al., 2013).

Similar to DSBs, DNA interstrand crosslinks (ICLs) are cytotoxic lesions that physically obstruct DNA replication and transcription. The Fanconi anemia (FA) pathway is responsible for repairing ICLs (Ceccaldi, Sarangi, & D'Andrea, 2016). A central step in the FA pathway involves the monoubiquitination of the FANCI/FANCD2 (ID) heterodimer at specific lysine residues (K523 of FANCI and K561 of FANCD2) (Swuec et al., 2017; Garcia-Higuera et al., 2001; Vandenberg et al., 2003). This monoubiquitination is carried out by the E3 ligase FANCL with the assistance of other FA-core complex components. Once monoubiquitinated, the ID complex recruits nucleases like FAN1, SLX4/SLX1, and XPF/ERCC1 to unhook the DNA crosslinks, facilitating downstream repair processes (Fontebasso, Etheridge, Oliver, Murray, & Carr, 2013; Garner & Smogorzewska, 2011; Yamamoto et al., 2011). After DNA damage, the monoubiquitinated and chromatin-bound ID complex is SUMOylated by PIAS1 and PIAS4. This DNA damage-induced SUMOylation triggers RNF4-dependent ubiquitylation of the ID complex. The SUMO-dependent polyubiquitin chains on the ID complex guide the DVC1-p97 ubiquitin-selective segregase complex for the active removal of the ID complex from chromatin (Gibbs-Seymour et al., 2015). Notably, recent clinical research on FA patients has shown that FANCA undergoes SUMOylation and subsequent RNF4-dependent ubiquitination and proteasome-mediated degradation in the absence of FAAP20 binding (Xie et al., 2015). This SUMO-ubiquitin signaling circuitry is also critical for the proper turnover of FANCA from damage sites in the normal FA pathway.

Covalent DNA–protein crosslinks (DPCs) are highly toxic DNA lesions that disrupt nearly all chromatin-based processes due to their large size (Fu et al., 2011; Nakano et al., 2013; Weickert & Stingele, 2022). DPCs are commonly induced by widely used chemotherapeutics, such as DNA topoisomerase inhibitors and Poly (ADP-ribose) polymerase (PARP) inhibitors (Kojima et al., 2020; Sun, Chen, & Pommier, 2023; Thomas & Pommier, 2019). The repair of DPCs involves the coordination of Tyrosyl-DNA phosphodiesterases (TDPs), the MRE11–RAD50–NBS1 (MRN) nuclease complex, and the protease SPRTN (also known as DVC1) (Stingele, Bellelli, & Boulton, 2017). Moreover, SUMO-mediated ubiquitination has been associated with the degradation of topoisomerase DNA-protein crosslinks (TOP-DPCs). TOP-DPCs undergo SUMOylation by PIAS4 and are then targeted by RNF4 for ubiquitination, which triggers the proteasomal degradation of TOP-DPCs (Sun et al., 2020). Similarly, trapped PARP1, a product of clinical PARP inhibitors (PARPi), is sequentially SUMOylated by PIAS4 and ubiquitinated by RNF4. The ubiquitin-dependent ATPase p97 recognizes and removes trapped PARP1 from chromatin (Krastev et al., 2022).

4.3. *Regulation of DNA replication and replication stress response*

The complete and accurate duplication of DNA is essential for maintaining genome integrity and ensuring the faithful transmission of genetic information. Active DNA replication creates a SUMO-rich and Ub-poor environment, largely influenced by the replisome-enriched SUMO deubiquitinase USP7 (Lecona, Rodriguez-Acebes, Specks, Lopez-Contreras, Ruppen, Murga, Munoz, et al., 2016). Working in coordination with USP7, the ATPase p97 and its co-factor FAF1 (also known as UBXN3) play a role in the spatiotemporal removal of SUMOylated or ubiquitinated DNA replication factors (Besche, Haas, Gygi, & Goldberg, 2009). This process helps maintain the balance between SUMO and ubiquitin around the replisomes, thereby supporting accurate replication. Recent research has revealed that RNF4 collaborates with USP7 to replenish the nuclear ubiquitin pool necessary for complete DNA replication (Kumar et al., 2017; Lecona, Rodriguez-Acebes, Specks, Lopez-Contreras, Ruppen, Murga, Muñoz, et al., 2016).

DNA replication is constantly challenged by various sources of replication stress, both endogenous and exogenous, often leading to replication fork stalling. Failure to address these issues properly can result in genome instability (Taglialatela et al., 2017; Wang, Xu, & Egli, 2023). Cells have evolved a complex network of responses to cope with replication stress. One critical pathway is fork reversal, where blocked replication forks are unwound to form four-way junctions, a process common in higher eukaryotes. Fork reversal typically occurs in a two-step process. First, the RAD51 recombinase, along with fork

remodelers like SNF2-family DNA translocases (HLTF, ZRANB3, and SMARCAL1), initiates limited fork reversal, creating superhelical strain in the newly replicated sister chromatids (Ceballos & Heyer, 2011; Kramarz et al., 2017; Liu et al., 2023; Rickman & Smogorzewska, 2019; Taglialatela et al., 2017). Second, TOP2A resolves the topological barriers on the reversed fork. At the same time, TOP2A is SUMOylated by ZATT, a SUMO E3 ligase, at lysines 1228 and 1240 (Tian et al., 2021). Subsequently, the translocase PICH is recruited by the SUMOylated TOP2A to drive extensive fork reversal (Tian et al., 2021). However, uncontrolled fork reversal can expose fork structures to nucleases, potentially causing pathological degradation or cleavage of stalled forks. Interestingly, RNF4 accumulates at stalled forks and targets SUMOylated TOP2A for ubiquitination and subsequent degradation (Ding et al., 2022). This SUMO-ubiquitin signaling circuitry precisely regulates the extent of fork reversal and protects stalled forks.

4.4. Regulation of mitotic division

RNF4 plays a crucial role in chromosome alignment and spindle assembly, primarily by regulating the kinetochore CENPH-CENPI-CENPK complex. It achieves this by targeting polySUMOylated CENPI for proteasomal degradation in mammals, a critical step for kinetochore assembly. Notably, in this process, SENP6 and RNF4 act antagonistically to maintain CENPI homeostasis (Mukhopadhyay, Arnaoutov, & Dasso, 2010). Furthermore, RNF4 also controls the stability of the recruitment factor Mis18BP1 for CENP-A, which plays a crucial role in regulating centromere architecture by controlling the deposition and/or maintenance (Fu et al., 2019; Liebelt et al., 2019). In mammalian cells, it is probable that the dynamics of CENP-B at centromeres are directly under the regulation of SUMO-primed RNF4-dependent proteasomal degradation (Maalouf et al., 2018). This finding aligns with the identification of CENP-B as a primary target of SENP6 in proteomic studies (Liebelt et al., 2019; Wagner et al., 2019).

In terms of biochemical function, RNF4 shares functional similarities with the Slx5-Slx8 complex in S. cerevisiae (Lallemand-Breitenbach et al., 2008; Tatham et al., 2008). Notably, while depletion of RNF4 from HeLa cells did not result in any noticeable defects in chromosome alignment, mitotic timing, or mitotic checkpoint function, it significantly increased the occurrence of lagging chromosomes during anaphase, with a three-to six-fold rise observed when employing various siRNA oligos (van de Pasch et al., 2013). This underscores the conserved role of both Slx5-Slx8 and RNF4 in safeguarding genome integrity during mitosis (van de Pasch et al., 2013). In an experiment conducted by Masayuki and his colleagues, they observed the accumulation of RNF4 on mitotic chromosomes in HeLa cells following exposure to the DNA topoisomerase II inhibitor etoposide during mitosis. Depletion of RNF4 sensitized mitotic HeLa cells to etoposide and increased the number of cells with micronuclei (Saito et al., 2014). Conversely, deletion of RNF4 in chicken DT40 cells resulted in a significant increase in chromosome breaks. Six weeks after RNF4 deletion, the DNA content in $RNF4^{-/-}$ cells decreased by 25%. Furthermore, $RNF4^{-/-}$ cells exhibited micronuclei, indicating abnormal chromosome segregation (Hirota et al., 2014). Collectively, these findings underscore the significance of RNF4 in preserving chromosome integrity by ensuring precise chromosome segregation during mitosis.

5. RNF111 and its role in genome maintenance

RNF111, also known as Arkadia, is an E3 ligase characterized by multiple N-terminal nuclear localization signals, three tandem SIMs, and a C-terminal RING-finger domain (Erker et al., 2013; Kotter, Mootz, & Heuer, 2023; Sun & Hunter, 2012). Originally identified as a key regulator in embryonic development, RNF111 was found to play a crucial role in activating and amplifying TGF-β family signaling by ubiquitinating and degrading negative regulators of the TGF-β pathway, including Smad7, SnoN, and c-Ski (Chen et al., 2015; Cunnington, Nazari, & Dixon, 2009; Koinuma et al., 2003; Liu et al., 2006; Nagano et al., 2007; Tian et al., 2015; Wu et al., 2021; Xu et al., 2021).

In 2012, RNF111's significance expanded as it was discovered to contain clustered SIMs through bioinformatics analysis, hinting at a new role in regulating SUMO-mediated signaling (Sun & Hunter, 2012). Subsequently, two independent research groups almost simultaneously reported RNF111's function as a STUbL, with roles in modulating PML homeostasis and nucleotide excision repair (NER) (Erker et al., 2013; Poulsen et al., 2013). In brief, RNF111 interacts with polySUMOylated PML through its tandem SIMs and catalyzes K48-linked ubiquitination of SUMOylated PML, leading to its degradation (Erker et al., 2013). Depletion of RNF111 results in the accumulation of SUMOylated PML, especially in response to arsenic exposure. Notably, RNF111 operates independently of RNF4 in PML degradation, underscoring the importance of these two STUbLs in the precise regulation of PML turnover (Erker et al., 2013; McIntosh, Walters, Arinze, & Davis, 2018; Sriramachandran et al., 2019). In contrast to its role with PML, RNF111 promotes K63-linked ubiquitin chain formation on SUMOylated xeroderma pigmentosum complementation group C (XPC) in response to UV radiation, with the assistance of UBC13-MMS2 (Poulsen et al., 2013; van Cuijk et al., 2015). This SUMO-dependent and non-proteolytic ubiquitination of XPC by RNF111 facilitates the release of XPC, enabling the loading of XPG and XPF-ERCC1 for efficient NER (Poulsen et al., 2013; van Cuijk et al., 2015). Additionally, RNF111 acts as a STUbL to mediate the displacement of polySUMOylated DNA polymerase η (Pol η) from damaged sites (Guerillon, Smedegaard, Hendriks, Nielsen, & Mailand, 2020). Interestingly, RNF4 also plays a role in restraining the DNA damage-induced accumulation of Pol η, independent of its STUbL activity (Guerillon et al., 2020).

Similar to the dimeric RNF4, the monomeric RING domain of RNF111 efficiently facilitates ubiquitin transfer. Structural and biochemical analyses have revealed that the monomeric RING domain of RNF111 binds non-covalently to free ubiquitin (Guerillon et al., 2020; Laigle et al., 2021; Nagano et al., 2007). Interestingly, RNF111 preferentially targets substrates carrying hybrid SUMO1-capped SUMO2/3 chains (Birkou et al., 2017; Episkopou et al., 2001; Erker et al., 2013). In a recent research, UBXN7, a member of the UBA-UBX family, was discovered to directly interact with the RING domain of RNF111 through its UAS thioredoxin-like domain. UBXN7 regulates the E3 ligase activity of RNF111 by competitively binding to its RING domain in competition with the E2 conjugating enzymes (Amhaz et al., 2023). Since UBXN7 is a co-factor of p97, RNF111 may potentially enhance the efficiency of protein clearance by p97, similar to the role played by RNF4 (Alexandru et al., 2008; Kochenova, Mukkavalli, Raman, & Walter, 2022; Tarcan, Poovathumkadavil, Skagia, & Gambus, 2022).

Furthermore, RNF111 contributes to the DNA damage response by acting as a NEDD8 E3 ligase in collaboration with UBE2M (Li et al., 2021; Ma et al., 2013). It facilitates the neddylation of histone H4 at DSB sites, which is then recognized by the MIU (Motif Interacting with Ubiquitin) domain of RNF168 (Ma et al., 2013; Pinato et al., 2009; Pinato, Gatti, Scandiuzzi, Confalonieri, & Penengo, 2011). This amplifies the DNA damage-induced ubiquitination cascade and promotes DNA damage repair. RNF111-mediated neddylation also inhibits DNA end resection, a critical process in DSB repair pathway choice (Jimeno et al., 2015; Li et al., 2021; Ma et al., 2013).

Despite being recognized as a STUbL for a decade, RNF111's substrates have been relatively limited. Due to the E3 ligase activity of NEDD8, it remains unclear whether RNF111 regulates the crosstalk between SUMO and NEDD8.

6. Conclusions and perspectives

Despite significant progress in understanding human STUbLs, their functions and substrates remain largely unexplored. There is a growing body of evidence suggesting that the nuclear periphery plays a spatiotemporal role in regulating DNA replication and repair, a phenomenon

conserved from yeast to humans. Yeast STUbLs have been shown to facilitate the relocation of damaged DNA to the nuclear periphery for proper repair. Investigating whether human STUbLs also play a role in modulating the relocalization of lesions to the nuclear periphery is a promising avenue of research.

Additionally, STUbLs frequently function within specialized compartments, such as nuclear repair foci that contain numerous DDR proteins. Recent research has uncovered that the SUMO/RNF4 pathway is activated by SLX4 compartmentalization (Alghoul et al., 2023). Whether a similar mechanism holds true for RNF111 remains uncertain. Investigating whether the STUbL pathway is regulated by other condensates is also a valuable avenue for future research.

Declaration of competing interest

The authors declare no competing interests.

Acknowledgements

We apologize to colleagues whose work could not be cited because of space limitations. This work was supported by National Key Research and Development Program of China (2022YFA1302800 and 2021YFA1101000), National Natural Science Foundation of China (31961160725, 31730021, 31971220, and 32170730), Fok Ying Tung Education Foundation, Fundamental Research Funds for the Zhejiang Provincial Universities (2021XZZX039), National Natural Science Foundation of Shaanxi Province [2023-JC-QN-0942].

References

Abed, M., Barry, K. C., Kenyagin, D., Koltun, B., Phippen, T. M., Delrow, J. J., et al. (2011). Degringolade, a SUMO-targeted ubiquitin ligase, inhibits Hairy/Groucho-mediated repression. *The EMBO Journal, 30*(7), 1289–1301. https://doi.org/10.1038/emboj.2011.42

Alexandru, G., Graumann, J., Smith, G. T., Kolawa, N. J., Fang, R., & Deshaies, R. J. (2008). UBXD7 binds multiple ubiquitin ligases and implicates p97 in HIF1alpha turnover. *Cell, 134*(5), 804–816. https://doi.org/10.1016/j.cell.2008.06.048

Alghoul, E., Paloni, M., Takedachi, A., Urbach, S., Barducci, A., Gaillard, P. H., et al. (2023). Compartmentalization of the SUMO/RNF4 pathway by SLX4 drives DNA repair. *Molecular Cell, 83*(10), 1640–1658. https://doi.org/10.1016/j.molcel.2023.03.021

Amhaz, S., Boeda, B., Chouchene, M., Colasse, S., Dingli, F., Loew, D., et al. (2023). The UAS thioredoxin-like domain of UBXN7 regulates E3 ubiquitin ligase activity of RNF111/Arkadia. *BMC Biology, 21*(1), 73. https://doi.org/10.1186/s12915-023-01576-4

Bakhoum, S. F., Thompson, S. L., Manning, A. L., & Compton, D. A. (2009). Genome stability is ensured by temporal control of kinetochore-microtubule dynamics. *Nature Cell Biology, 11*(1), 27–35. https://doi.org/10.1038/ncb1809

Bergink, S., & Jentsch, S. (2009). Principles of ubiquitin and SUMO modifications in DNA repair. *Nature, 458*(7237), 461–467. https://doi.org/10.1038/nature07963

Besche, H. C., Haas, W., Gygi, S. P., & Goldberg, A. L. (2009). Isolation of mammalian 26S proteasomes and p97/VCP complexes using the ubiquitin-like domain from HHR23B reveals novel proteasome-associated proteins. *Biochemistry, 48*(11), 2538–2549. https://doi.org/10.1021/bi802198q

Birkou, M., Chasapis, C. T., Marousis, K. D., Loutsidou, A. K., Bentrop, D., Lelli, M., et al. (2017). A residue specific insight into the Arkadia E3 ubiquitin ligase activity and conformational plasticity. *Journal of Molecular Biology, 429*(15), 2373–2386. https://doi.org/10.1016/j.jmb.2017.06.012

Bouchard, D., Wang, W., Yang, W. C., He, S., Garcia, A., & Matunis, M. J. (2021). SUMO paralogue-specific functions revealed through systematic analysis of human knockout cell lines and gene expression data. *Molecular Biology of the Cell, 32*(19), 1849–1866. https://doi.org/10.1091/mbc.E21-01-0031

Boutell, C., Cuchet-Lourenco, D., Vanni, E., Orr, A., Glass, M., McFarlane, S., et al. (2011). A viral ubiquitin ligase has substrate preferential SUMO targeted ubiquitin ligase activity that counteracts intrinsic antiviral defence. *PLoS Pathogens, 7*(9), Article e1002245. https://doi.org/10.1371/journal.ppat.1002245

Branigan, E., Plechanovova, A., Jaffray, E. G., Naismith, J. H., & Hay, R. T. (2015). Structural basis for the RING-catalyzed synthesis of K63-linked ubiquitin chains. *Nature Structural & Molecular Biology, 22*(8), 597–602. https://doi.org/10.1038/nsmb.3052

Bremm, A., Freund, S. M., & Komander, D. (2010). Lys11-linked ubiquitin chains adopt compact conformations and are preferentially hydrolyzed by the deubiquitinase Cezanne. *Nature Structural & Molecular Biology, 17*(8), 939–947. https://doi.org/10.1038/nsmb.1873

Canela, A., Maman, Y., Jung, S., Wong, N., Callen, E., Day, A., et al. (2017). Genome organization drives chromosome fragility. *Cell, 170*(3), 507–521.e518. https://doi.org/10.1016/j.cell.2017.06.034

Castaneda, C. A., Dixon, E. K., Walker, O., Chaturvedi, A., Nakasone, M. A., Curtis, J. E., et al. (2016). Linkage via K27 bestows ubiquitin chains with unique properties among polyubiquitins. *Structure, 24*(3), 423–436. https://doi.org/10.1016/j.str.2016.01.007

Ceballos, S. J., & Heyer, W. D. (2011). Functions of the Snf2/Swi2 family Rad54 motor protein in homologous recombination. *Biochimica et Biophysica Acta, 1809*(9), 509–523. https://doi.org/10.1016/j.bbagrm.2011.06.006

Ceccaldi, R., Sarangi, P., & D'Andrea, A. D. (2016). The fanconi anaemia pathway: New players and new functions. *Nature Reviews Molecular Cell Biology, 17*(6), 337–349. https://doi.org/10.1038/nrm.2016.48

Cejka, P., & Symington, L. S. (2021). DNA end resection: Mechanism and control. *Annual Review of Genetics, 55*, 285–307. https://doi.org/10.1146/annurev-genet-071719-020312

Chang, H. R., Munkhjargal, A., Kim, M. J., Park, S. Y., Jung, E., Ryu, J. H., et al. (2018). The functional roles of PML nuclear bodies in genome maintenance. *Mutation Research, 809*, 99–107. https://doi.org/10.1016/j.mrfmmm.2017.05.002

Chang, Y. C., Oram, M. K., & Bielinsky, A. K. (2021). SUMO-targeted ubiquitin ligases and their functions in maintaining genome stability. *International Journal of Molecular Sciences, 22*(10). https://doi.org/10.3390/ijms22105391

Chapman, J. R., Taylor, M. R., & Boulton, S. J. (2012). Playing the end game: DNA double-strand break repair pathway choice. *Molecular Cell, 47*(4), 497–510. https://doi.org/10.1016/j.molcel.2012.07.029

Chen, I. (2016). New DUBs on the block. *Nature Structural & Molecular Biology, 23*(7), 623. https://doi.org/10.1038/nsmb.3261

Chen, H., Yang, T., Lei, Z., Wang, L., Yang, H., Tong, X., et al. (2015). RNF111/Arkadia is regulated by DNA methylation and affects TGF-beta/Smad signaling associated invasion in NSCLC cells. *Lung Cancer, 90*(1), 32–40. https://doi.org/10.1016/j.lungcan.2015.07.010

Chiariotti, L., Benvenuto, G., Fedele, M., Santoro, M., Simeone, A., Fusco, A., et al. (1998). Identification and characterization of a novel RING-finger gene (RNF4) mapping at 4p16.3. *Genomics, 47*(2), 258–265. https://doi.org/10.1006/geno.1997.5105

Ciccia, A., & Elledge, S. J. (2010). The DNA damage response: Making it safe to play with knives. *Molecular Cell, 40*(2), 179–204. https://doi.org/10.1016/j.molcel.2010.09.019

Corpet, A., Kleijwegt, C., Roubille, S., Juillard, F., Jacquet, K., Texier, P., et al. (2020). PML nuclear bodies and chromatin dynamics: Catch me if you can. *Nucleic Acids Research, 48*(21), 11890–11912. https://doi.org/10.1093/nar/gkaa828

van Cuijk, L., van Belle, G. J., Turkyilmaz, Y., Poulsen, S. L., Janssens, R. C., Theil, A. F., et al. (2015). SUMO and ubiquitin-dependent XPC exchange drives nucleotide excision repair. *Nature Communications, 6*, 7499. https://doi.org/10.1038/ncomms8499

Cunnington, R. H., Nazari, M., & Dixon, I. M. (2009). c-Ski, Smurf2, and Arkadia as regulators of TGF-beta signaling: new targets for managing myofibroblast function and cardiac fibrosis. *Canadian Journal of Physiology and Pharmacology, 87*(10), 764–772. https://doi.org/10.1139/Y09-076

David, R. (2011). DUBs' key to selectivity. *Nature Reviews Molecular Cell Biology, 13*(2), 64. https://doi.org/10.1038/nrm3268

Ding, L., Luo, Y., Tian, T., Chen, X., Yang, Y., Bu, M., et al. (2022). RNF4 controls the extent of replication fork reversal to preserve genome stability. *Nucleic Acids Research, 50*(10), 5672–5687. https://doi.org/10.1093/nar/gkac447

Dove, K. K., Kemp, H. A., Di Bona, K. R., Reiter, K. H., Milburn, L. J., Camacho, D., et al. (2017). Two functionally distinct E2/E3 pairs coordinate sequential ubiquitination of a common substrate in Caenorhabditis elegans development. *Proceedings of the National Academy of Sciences of the U S A, 114*(32), E6576–E6584. https://doi.org/10.1073/pnas.1705060114

Episkopou, V., Arkell, R., Timmons, P. M., Walsh, J. J., Andrew, R. L., & Swan, D. (2001). Induction of the mammalian node requires Arkadia function in the extraembryonic lineages. *Nature, 410*(6830), 825–830. https://doi.org/10.1038/35071095

Erker, Y., Neyret-Kahn, H., Seeler, J. S., Dejean, A., Atfi, A., & Levy, L. (2013). Arkadia, a novel SUMO-targeted ubiquitin ligase involved in PML degradation. *Molecular and Cellular Biology, 33*(11), 2163–2177. https://doi.org/10.1128/MCB.01019-12

Fontebasso, Y., Etheridge, T. J., Oliver, A. W., Murray, J. M., & Carr, A. M. (2013). The conserved Fanconi anemia nuclease Fan1 and the SUMO E3 ligase Pli1 act in two novel Pso2-independent pathways of DNA interstrand crosslink repair in yeast. *DNA Repair, 12*(12), 1011–1023. https://doi.org/10.1016/j.dnarep.2013.10.003

Fu, H., Liu, N., Dong, Q., Ma, C., Yang, J., Xiong, J., et al. (2019). SENP6-mediated M18BP1 deSUMOylation regulates CENP-A centromeric localization. *Cell Research, 29*(3), 254–257. https://doi.org/10.1038/s41422-018-0139-y

Fu, Y. V., Yardimci, H., Long, D. T., Ho, T. V., Guainazzi, A., Bermudez, V. P., et al. (2011). Selective bypass of a lagging strand roadblock by the eukaryotic replicative DNA helicase. *Cell, 146*(6), 931–941. https://doi.org/10.1016/j.cell.2011.07.045

Galanty, Y., Belotserkovskaya, R., Coates, J., & Jackson, S. P. (2012). RNF4, a SUMO-targeted ubiquitin E3 ligase, promotes DNA double-strand break repair. *Genes & Development, 26*(11), 1179–1195. https://doi.org/10.1101/gad.188284.112

Garcia-Higuera, I., Taniguchi, T., Ganesan, S., Meyn, M. S., Timmers, C., Hejna, J., … D'Andrea, A. D. (2001). Interaction of the Fanconi anemia proteins and BRCA1 in a common pathway. *Molecular Cell, 7*(2), 249–262. https://doi.org/10.1016/s1097-2765(01)00173-3

Garner, E., & Smogorzewska, A. (2011). Ubiquitylation and the Fanconi anemia pathway. *FEBS Letters, 585*(18), 2853–2860. https://doi.org/10.1016/j.febslet.2011.04.078

Garvin, A. J., Walker, A. K., Densham, R. M., Chauhan, A. S., Stone, H. R., Mackay, H. L., et al. (2019). The deSUMOylase SENP2 coordinates homologous recombination and nonhomologous end joining by independent mechanisms. *Genes & Development, 33*(5–6), 333–347. https://doi.org/10.1101/gad.321125.118

Gatel, P., Piechaczyk, M., & Bossis, G. (2020). Ubiquitin, SUMO, and Nedd8 as therapeutic targets in cancer. *Advances in Experimental Medicine & Biology, 1233*, 29–54. https://doi.org/10.1007/978-3-030-38266-7_2

Gibbs-Seymour, I., Oka, Y., Rajendra, E., Weinert, B. T., Passmore, L. A., Patel, K. J., et al. (2015). Ubiquitin-SUMO circuitry controls activated fanconi anemia ID complex dosage in response to DNA damage. *Molecular Cell, 57*(1), 150–164. https://doi.org/10.1016/j.molcel.2014.12.001

Gill, G. (2004). SUMO and ubiquitin in the nucleus: Different functions, similar mechanisms? *Genes & Development, 18*(17), 2046–2059. https://doi.org/10.1101/gad.1214604

Groocock, L. M., Nie, M., Prudden, J., Moiani, D., Wang, T., Cheltsov, A., et al. (2014). RNF4 interacts with both SUMO and nucleosomes to promote the DNA damage response. *EMBO Reports, 15*(5), 601–608. https://doi.org/10.1002/embr.201338369

Guerillon, C., Smedegaard, S., Hendriks, I. A., Nielsen, M. L., & Mailand, N. (2020). Multisite SUMOylation restrains DNA polymerase eta interactions with DNA damage sites. *Journal of Biological Chemistry, 295*(25), 8350–8362. https://doi.org/10.1074/jbc.RA120.013780

Guo, L., Giasson, B. I., Glavis-Bloom, A., Brewer, M. D., Shorter, J., Gitler, A. D., et al. (2014). A cellular system that degrades misfolded proteins and protects against neurodegeneration. *Molecular Cell, 55*(1), 15–30. https://doi.org/10.1016/j.molcel.2014.04.030

Guzzo, C. M., Berndsen, C. E., Zhu, J., Gupta, V., Datta, A., Greenberg, R. A., et al. (2012). RNF4-dependent hybrid SUMO-ubiquitin chains are signals for RAP80 and thereby mediate the recruitment of BRCA1 to sites of DNA damage. *Science Signaling, 5*(253), ra88. https://doi.org/10.1126/scisignal.2003485

Hanahan, D. (2022). Hallmarks of cancer: New dimensions. *Cancer Discovery, 12*(1), 31–46. https://doi.org/10.1158/2159-8290.CD-21-1059

Hanahan, D., & Weinberg, R. A. (2011). Hallmarks of cancer: The next generation. *Cell, 144*(5), 646–674. https://doi.org/10.1016/j.cell.2011.02.013

Han, J., Wan, L., Jiang, G., Cao, L., Xia, F., Tian, T., et al. (2021). ATM controls the extent of DNA end resection by eliciting sequential posttranslational modifications of CtIP. *Proceedings of the National Academy of Sciences of the U S A, 118*(12). https://doi.org/10.1073/pnas.2022600118

Hay, R. T. (2007). SUMO-Specific proteases: A twist in the tail. *Trends in Cell Biology, 17*(8), 370–376. https://doi.org/10.1016/j.tcb.2007.08.002

Hickey, C. M., Wilson, N. R., & Hochstrasser, M. (2012). Function and regulation of SUMO proteases. *Nature Reviews Molecular Cell Biology, 13*(12), 755–766. https://doi.org/10.1038/nrm3478

Hirota, K., Tsuda, M., Murai, J., Takagi, T., Keka, I. S., Narita, T., et al. (2014). SUMO-targeted ubiquitin ligase RNF4 plays a critical role in preventing chromosome loss. *Genes to Cells, 19*(10), 743–754. https://doi.org/10.1111/gtc.12173

Hoege, C., Pfander, B., Moldovan, G. L., Pyrowolakis, G., & Jentsch, S. (2002). RAD6-dependent DNA repair is linked to modification of PCNA by ubiquitin and SUMO. *Nature, 419*(6903), 135–141. https://doi.org/10.1038/nature00991

Huang, X., Yang, Y., Zhu, D., Zhao, Y., Wei, M., Li, K., et al. (2022). PRMT5-mediated RNF4 methylation promotes therapeutic resistance of APL cells to As(2)O(3) by stabilizing oncoprotein PML-RARalpha. *Cellular and Molecular Life Sciences, 79*(6), 319. https://doi.org/10.1007/s00018-022-04358-3

Hu, X. V., Rodrigues, T. M., Tao, H., Baker, R. K., Miraglia, L., Orth, A. P., et al. (2010). Identification of RING finger protein 4 (RNF4) as a modulator of DNA demethylation through a functional genomics screen. *Proceedings of the National Academy of Sciences of the U S A, 107*(34), 15087–15092. https://doi.org/10.1073/pnas.1009025107

Jackson, S. P., & Bartek, J. (2009). The DNA-damage response in human biology and disease. *Nature, 461*(7267), 1071–1078. https://doi.org/10.1038/nature08467

Jalal, D., Chalissery, J., & Hassan, A. H. (2017). Genome maintenance in Saccharomyces cerevisiae: The role of SUMO and SUMO-targeted ubiquitin ligases. *Nucleic Acids Research, 45*(5), 2242–2261. https://doi.org/10.1093/nar/gkw1369

Jansen, N. S., & Vertegaal, A. C. O. (2021). A chain of events: Regulating target proteins by SUMO polymers. *Trends in Biochemical Sciences, 46*(2), 113–123. https://doi.org/10.1016/j.tibs.2020.09.002

Jasin, M., & Rothstein, R. (2013). Repair of strand breaks by homologous recombination. *Cold Spring Harbor Perspectives in Biology, 5*(11), Article a012740. https://doi.org/10.1101/cshperspect.a012740

Jeggo, P. A., Pearl, L. H., & Carr, A. M. (2016). DNA repair, genome stability and cancer: A historical perspective. *Nature Reviews Cancer, 16*(1), 35–42. https://doi.org/10.1038/nrc.2015.4

Jimeno, S., Fernandez-Avila, M. J., Cruz-Garcia, A., Cepeda-Garcia, C., Gomez-Cabello, D., & Huertas, P. (2015). Neddylation inhibits CtIP-mediated resection and regulates DNA double strand break repair pathway choice. *Nucleic Acids Research, 43*(2), 987–999. https://doi.org/10.1093/nar/gku1384

Joazeiro, C. A., & Weissman, A. M. (2000). RING finger proteins: Mediators of ubiquitin ligase activity. *Cell, 102*(5), 549–552. https://doi.org/10.1016/s0092-8674(00)00077-5

Johnson, E. S. (2004). Protein modification by SUMO. *Annual Review of Biochemistry, 73*, 355–382. https://doi.org/10.1146/annurev.biochem.73.011303.074118

Jung, J. W., Bae, S. J., Kang, G. Y., Kim, K. H., Yeo, W. S., Park, S. H., et al. (2013). Analysis of the biochemical role of Lys-11 in polyubiquitin chain formation using quantitative mass spectrometry. *Rapid Communications in Mass Spectrometry, 27*(2), 339–346. https://doi.org/10.1002/rcm.6447

Katsuki, Y., Jeggo, P. A., Uchihara, Y., Takata, M., & Shibata, A. (2020). DNA double-strand break end resection: A critical relay point for determining the pathway of repair and signaling. *Genome Instability & Disease, 1*(4), 155–171. https://doi.org/10.1007/s42764-020-00017-8

Keiten-Schmitz, J., Wagner, K., Piller, T., Kaulich, M., Alberti, S., & Muller, S. (2020). The nuclear SUMO-targeted ubiquitin quality control network regulates the dynamics of cytoplasmic stress granules. *Molecular Cell, 79*(1), 54–67. https://doi.org/10.1016/j.molcel.2020.05.017

Keusekotten, K., Bade, V. N., Meyer-Teschendorf, K., Sriramachandran, A. M., Fischer-Schrader, K., Krause, A., … Praefcke, G. J. (2014). Multivalent interactions of the SUMO-interaction motifs in RING finger protein 4 determine the specificity for chains of the SUMO. *Biochemical Journal, 457*(1), 207–214. https://doi.org/10.1042/BJ20130753

Kim, H. T., Kim, K. P., Lledias, F., Kisselev, A. F., Scaglione, K. M., Skowyra, D., et al. (2007). Certain pairs of ubiquitin-conjugating enzymes (E2s) and ubiquitin-protein ligases (E3s) synthesize nondegradable forked ubiquitin chains containing all possible isopeptide linkages. *Journal of Biological Chemistry, 282*(24), 17375–17386. https://doi.org/10.1074/jbc.M609659200

Kochenova, O. V., Mukkavalli, S., Raman, M., & Walter, J. C. (2022). Cooperative assembly of p97 complexes involved in replication termination. *Nature Communications, 13*(1), 6591. https://doi.org/10.1038/s41467-022-34210-y

Koinuma, D., Shinozaki, M., Komuro, A., Goto, K., Saitoh, M., Hanyu, A., et al. (2003). Arkadia amplifies TGF-beta superfamily signalling through degradation of Smad7. *The EMBO Journal, 22*(24), 6458–6470. https://doi.org/10.1093/emboj/cdg632

Kojima, Y., Machida, Y., Palani, S., Caulfield, T. R., Radisky, E. S., Kaufmann, S. H., et al. (2020). FAM111A protects replication forks from protein obstacles via its trypsin-like domain. *Nature Communications, 11*(1), 1318. https://doi.org/10.1038/s41467-020-15170-7

Kosoy, A., Calonge, T. M., Outwin, E. A., & O'Connell, M. J. (2007). Fission yeast Rnf4 homologs are required for DNA repair. *Journal of Biological Chemistry, 282*(28), 20388–20394. https://doi.org/10.1074/jbc.M702652200

Kotter, A., Mootz, H. D., & Heuer, A. (2023). Conformational and interface variability in multivalent SIM-SUMO interaction. *Journal of Physical Chemistry B, 127*(17), 3806–3815. https://doi.org/10.1021/acs.jpcb.2c08760

Kramarz, K., Mucha, S., Litwin, I., Barg-Wojas, A., Wysocki, R., & Dziadkowiec, D. (2017). DNA damage tolerance pathway choice through Uls1 modulation of Srs2 SUMOylation in Saccharomyces cerevisiae. *Genetics, 206*(1), 513–525. https://doi.org/10.1534/genetics.116.196568

Krastev, D. B., Li, S., Sun, Y., Wicks, A. J., Hoslett, G., Weekes, D., et al. (2022). The ubiquitin-dependent ATPase p97 removes cytotoxic trapped PARP1 from chromatin. *Nature Cell Biology, 24*(1), 62–73. https://doi.org/10.1038/s41556-021-00807-6

Kumar, R., Gonzalez-Prieto, R., Xiao, Z., Verlaan-de Vries, M., & Vertegaal, A. C. O. (2017). The STUbL RNF4 regulates protein group SUMOylation by targeting the SUMO conjugation machinery. *Nature Communications, 8*(1), 1809. https://doi.org/10.1038/s41467-017-01900-x

Kuo, C. Y., Li, X., Kong, X. Q., Luo, C., Chang, C. C., Chung, Y., et al. (2014). An arginine-rich motif of ring finger protein 4 (RNF4) oversees the recruitment and degradation of the phosphorylated and SUMOylated Kruppel-associated box domain-associated protein 1 (KAP1)/TRIM28 protein during genotoxic stress. *Journal of Biological Chemistry, 289*(30), 20757–20772. https://doi.org/10.1074/jbc.M114.555672

Laigle, V., Dingli, F., Amhaz, S., Perron, T., Chouchene, M., Colasse, S., et al. (2021). Quantitative ubiquitylome analysis reveals the specificity of rnf111/arkadia E3 ubiquitin ligase for its degradative substrates SKI and SKIL/SnoN in TGF-beta signaling pathway. *Molecular & Cellular Proteomics, 20*, Article 100173. https://doi.org/10.1016/j.mcpro.2021.100173

Lallemand-Breitenbach, V., Jeanne, M., Benhenda, S., Nasr, R., Lei, M., Peres, L., et al. (2008). Arsenic degrades PML or PML-RARalpha through a SUMO-triggered RNF4/ubiquitin-mediated pathway. *Nature Cell Biology, 10*(5), 547–555. https://doi.org/10.1038/ncb1717

Lecona, E., Rodriguez-Acebes, S., Specks, J., Lopez-Contreras, A. J., Ruppen, I., Murga, M., et al. (2016). USP7 is a SUMO deubiquitinase essential for DNA replication. *Nature Structural & Molecular Biology, 23*(4), 270–277. https://doi.org/10.1038/nsmb.3185

Lee, J. M., Hammaren, H. M., Savitski, M. M., & Baek, S. H. (2023). Control of protein stability by post-translational modifications. *Nature Communications, 14*(1), 201. https://doi.org/10.1038/s41467-023-35795-8

Liebelt, F., Jansen, N. S., Kumar, S., Gracheva, E., Claessens, L. A., Verlaan-de Vries, M., et al. (2019). The poly-SUMO2/3 protease SENP6 enables assembly of the constitutive centromere-associated network by group deSUMOylation. *Nature Communications, 10*(1), 3987. https://doi.org/10.1038/s41467-019-11773-x

Liew, C. W., Sun, H., Hunter, T., & Day, C. L. (2010). RING domain dimerization is essential for RNF4 function. *Biochemical Journal, 431*(1), 23–29. https://doi.org/10.1042/BJ20100957

Liu, W., Rui, H., Wang, J., Lin, S., He, Y., Chen, M., et al. (2006). Axin is a scaffold protein in TGF-beta signaling that promotes degradation of Smad7 by Arkadia. *The EMBO Journal, 25*(8), 1646–1658. https://doi.org/10.1038/sj.emboj.7601057

Liu, W., Saito, Y., Jackson, J., Bhowmick, R., Kanemaki, M. T., Vindigni, A., et al. (2023). RAD51 bypasses the CMG helicase to promote replication fork reversal. *Science, 380*(6643), 382–387. https://doi.org/10.1126/science.add7328

Li, C., Zhang, L., Qian, D., Cheng, M., Hu, H., Hong, Z., et al. (2021). RNF111-facilitated neddylation potentiates cGAS-mediated antiviral innate immune response. *PLoS Pathogens, 17*(3), Article e1009401. https://doi.org/10.1371/journal.ppat.1009401

Locke, A. J., Hossain, L., McCrostie, G., Ronato, D. A., Fitieh, A., Rafique, T. A., et al. (2021). SUMOylation mediates CtIP's functions in DNA end resection and replication fork protection. *Nucleic Acids Research, 49*(2), 928–953. https://doi.org/10.1093/nar/gkaa1232

Lombard, D. B., Chua, K. F., Mostoslavsky, R., Franco, S., Gostissa, M., & Alt, F. W. (2005). DNA repair, genome stability, and aging. *Cell, 120*(4), 497–512. https://doi.org/10.1016/j.cell.2005.01.028

Luo, K., Deng, M., Li, Y., Wu, C., Xu, Z., Yuan, J., et al. (2015). CDK-mediated RNF4 phosphorylation regulates homologous recombination in S-phase. *Nucleic Acids Research, 43*(11), 5465–5475. https://doi.org/10.1093/nar/gkv434

Luo, K., Zhang, H., Wang, L., Yuan, J., & Lou, Z. (2012). Sumoylation of MDC1 is important for proper DNA damage response. *The EMBO Journal, 31*(13), 3008–3019. https://doi.org/10.1038/emboj.2012.158

Maalouf, J. E., Texier, P., Erliandri, I., Cohen, C., Corpet, A., Catez, F., et al. (2018). CENP-B dynamics at centromeres is regulated by a SUMOylation/ubiquitination and proteasomal-dependent degradation mechanism involving the SUMO-targeted ubiquitin E3 ligase RNF4. *bioRxiv*. , Article 245597. https://doi.org/10.1101/245597

Ma, T., Chen, Y., Zhang, F., Yang, C. Y., Wang, S., & Yu, X. (2013). RNF111-dependent neddylation activates DNA damage-induced ubiquitination. *Molecular Cell, 49*(5), 897–907. https://doi.org/10.1016/j.molcel.2013.01.006

MacNeill, S. A. (2005). Genome stability: A self-sufficient DNA repair machine. *Current Biology, 15*(1), R21–R23. https://doi.org/10.1016/j.cub.2004.12.014

Maspero, E., & Polo, S. (2016). In vitro ubiquitination: Self-ubiquitination, chain formation, and substrate ubiquitination assays. *Methods in Molecular Biology, 1449*, 153–160. https://doi.org/10.1007/978-1-4939-3756-1_7

Maure, J. F., Moser, S. C., Jaffray, E. G., A, F. A., & Hay, R. T. (2016). Loss of ubiquitin E2 Ube2w rescues hypersensitivity of Rnf4 mutant cells to DNA damage. *Scientific Reports, 6*, Article 26178. https://doi.org/10.1038/srep26178

McIntosh, D. J., Walters, T. S., Arinze, I. J., & Davis, J. (2018). Arkadia (RING finger protein 111) mediates sumoylation-dependent stabilization of Nrf2 through K48-linked ubiquitination. *Cellular Physiology and Biochemistry, 46*(1), 418–430. https://doi.org/10.1159/000488475

Millan-Zambrano, G., Burton, A., Bannister, A. J., & Schneider, R. (2022). Histone post-translational modifications - cause and consequence of genome function. *Nature Reviews Genetics, 23*(9), 563–580. https://doi.org/10.1038/s41576-022-00468-7

Moilanen, A. M., Poukka, H., Karvonen, U., Hakli, M., Janne, O. A., & Palvimo, J. J. (1998). Identification of a novel RING finger protein as a coregulator in steroid receptor-mediated gene transcription. *Molecular and Cellular Biology, 18*(9), 5128–5139. https://doi.org/10.1128/MCB.18.9.5128

Moriyama, T., Fujimitsu, Y., Yoshikai, Y., Sasano, T., Yamada, K., Murakami, M., et al. (2014). SUMO-modification and elimination of the active DNA demethylation enzyme TDG in cultured human cells. *Biochemical and Biophysical Research Communications, 447*(3), 419–424. https://doi.org/10.1016/j.bbrc.2014.04.004

Mukhopadhyay, D., Arnaoutov, A., & Dasso, M. (2010). The SUMO protease SENP6 is essential for inner kinetochore assembly. *The Journal of Cell Biology, 188*(5), 681–692. https://doi.org/10.1083/jcb.200909008

Mukhopadhyay, D., & Dasso, M. (2007). Modification in reverse: The SUMO proteases. *Trends in Biochemical Sciences, 32*(6), 286–295. https://doi.org/10.1016/j.tibs.2007.05.002

Munk, S., Sigurethsson, J. O., Xiao, Z., Batth, T. S., Franciosa, G., von Stechow, L., et al. (2017). Proteomics reveals global regulation of protein SUMOylation by ATM and ATR kinases during replication stress. *Cell Reports, 21*(2), 546–558. https://doi.org/10.1016/j.celrep.2017.09.059

Nagano, Y., Mavrakis, K. J., Lee, K. L., Fujii, T., Koinuma, D., Sase, H., et al. (2007). Arkadia induces degradation of SnoN and c-Ski to enhance transforming growth factor-beta signaling. *Journal of Biological Chemistry, 282*(28), 20492–20501. https://doi.org/10.1074/jbc.M701294200

Nakano, T., Miyamoto-Matsubara, M., Shoulkamy, M. I., Salem, A. M., Pack, S. P., Ishimi, Y., et al. (2013). Translocation and stability of replicative DNA helicases upon encountering DNA-protein cross-links. *Journal of Biological Chemistry, 288*(7), 4649–4658. https://doi.org/10.1074/jbc.M112.419358

Okuma, T., Honda, R., Ichikawa, G., Tsumagari, N., & Yasuda, H. (1999). In vitro SUMO-1 modification requires two enzymatic steps, E1 and E2. *Biochemical and Biophysical Research Communications, 254*(3), 693–698. https://doi.org/10.1006/bbrc.1998.9995

Pao, K. C., Wood, N. T., Knebel, A., Rafie, K., Stanley, M., Mabbitt, P. D., et al. (2018). Activity-based E3 ligase profiling uncovers an E3 ligase with esterification activity. *Nature, 556*(7701), 381–385. https://doi.org/10.1038/s41586-018-0026-1

Parker, J. L., & Ulrich, H. D. (2012). A SUMO-interacting motif activates budding yeast ubiquitin ligase Rad18 towards SUMO-modified PCNA. *Nucleic Acids Research, 40*(22), 11380–11388. https://doi.org/10.1093/nar/gks892

van de Pasch, L. A., Miles, A. J., Nijenhuis, W., Brabers, N. A., van Leenen, D., Lijnzaad, P., et al. (2013). Centromere binding and a conserved role in chromosome stability for SUMO-dependent ubiquitin ligases. *PLoS One, 8*(6), Article e65628. https://doi.org/10.1371/journal.pone.0065628

Peng, C., Trojanowski, J. Q., & Lee, V. M. (2020). Protein transmission in neurodegenerative disease. *Nature Reviews Neurology, 16*(4), 199–212. https://doi.org/10.1038/s41582-020-0333-7

Perry, J. J., Tainer, J. A., & Boddy, M. N. (2008). A SIM-ultaneous role for SUMO and ubiquitin. *Trends in Biochemical Sciences, 33*(5), 201–208. https://doi.org/10.1016/j.tibs.2008.02.001

Pfeiffer, A., Luijsterburg, M. S., Acs, K., Wiegant, W. W., Helfricht, A., Herzog, L. K., et al. (2017). Ataxin-3 consolidates the MDC1-dependent DNA double-strand break response by counteracting the SUMO-targeted ubiquitin ligase RNF4. *The EMBO Journal, 36*(8), 1066–1083. https://doi.org/10.15252/embj.201695151

Pilie, P. G., Tang, C., Mills, G. B., & Yap, T. A. (2019). State-of-the-art strategies for targeting the DNA damage response in cancer. *Nature Reviews Clinical Oncology, 16*(2), 81–104. https://doi.org/10.1038/s41571-018-0114-z

Pinato, S., Gatti, M., Scandiuzzi, C., Confalonieri, S., & Penengo, L. (2011). UMI, a novel RNF168 ubiquitin binding domain involved in the DNA damage signaling pathway. *Molecular and Cellular Biology, 31*(1), 118–126. https://doi.org/10.1128/MCB.00818-10

Pinato, S., Scandiuzzi, C., Arnaudo, N., Citterio, E., Gaudino, G., & Penengo, L. (2009). RNF168, a new RING finger, MIU-containing protein that modifies chromatin by ubiquitination of histones H2A and H2AX. *BMC Molecular Biology, 10*, 55. https://doi.org/10.1186/1471-2199-10-55

Plechanovova, A., Jaffray, E. G., McMahon, S. A., Johnson, K. A., Navratilova, I., Naismith, J. H., et al. (2011). Mechanism of ubiquitylation by dimeric RING ligase RNF4. *Nature Structural & Molecular Biology, 18*(9), 1052–1059. https://doi.org/10.1038/nsmb.2108

Poulsen, S. L., Hansen, R. K., Wagner, S. A., van Cuijk, L., van Belle, G. J., Streicher, W., et al. (2013). RNF111/Arkadia is a SUMO-targeted ubiquitin ligase that facilitates the DNA damage response. *The Journal of Cell Biology, 201*(6), 797–807. https://doi.org/10.1083/jcb.201212075

Prudden, J., Pebernard, S., Raffa, G., Slavin, D. A., Perry, J. J., Tainer, J. A., et al. (2007). SUMO-targeted ubiquitin ligases in genome stability. *The EMBO Journal, 26*(18), 4089–4101. https://doi.org/10.1038/sj.emboj.7601838

Ragland, R. L., Patel, S., Rivard, R. S., Smith, K., Peters, A. A., Bielinsky, A. K., et al. (2013). RNF4 and PLK1 are required for replication fork collapse in ATR-deficient cells. *Genes & Development, 27*(20), 2259–2273. https://doi.org/10.1101/gad.223180.113

Rickman, K., & Smogorzewska, A. (2019). Advances in understanding DNA processing and protection at stalled replication forks. *The Journal of Cell Biology, 218*(4), 1096–1107. https://doi.org/10.1083/jcb.201809012

Rojas-Fernandez, A., Plechanovova, A., Hattersley, N., Jaffray, E., Tatham, M. H., & Hay, R. T. (2014). SUMO chain-induced dimerization activates RNF4. *Molecular Cell, 53*(6), 880–892. https://doi.org/10.1016/j.molcel.2014.02.031

Ross, C. A., & Poirier, M. A. (2004). Protein aggregation and neurodegenerative disease. *Nature Medicine, 10*(Suppl), S10–S17. https://doi.org/10.1038/nm1066

Saeki, Y. (2017). Ubiquitin recognition by the proteasome. *Journal of Biochemistry, 161*(2), 113–124. https://doi.org/10.1093/jb/mvw091

Sahin, U., Ferhi, O., Jeanne, M., Benhenda, S., Berthier, C., Jollivet, F., et al. (2014). Oxidative stress-induced assembly of PML nuclear bodies controls sumoylation of partner proteins. *The Journal of Cell Biology, 204*(6), 931–945. https://doi.org/10.1083/jcb.201305148

Saito, M., Fujimitsu, Y., Sasano, T., Yoshikai, Y., Ban-Ishihara, R., Nariai, Y., et al. (2014). The SUMO-targeted ubiquitin ligase RNF4 localizes to etoposide-exposed mitotic chromosomes: Implication for a novel DNA damage response during mitosis. *Biochemical and Biophysical Research Communications, 447*(1), 83–88. https://doi.org/10.1016/j.bbrc.2014.03.106

Schumacher, B., Pothof, J., Vijg, J., & Hoeijmakers, J. H. J. (2021). The central role of DNA damage in the ageing process. *Nature, 592*(7856), 695–703. https://doi.org/10.1038/s41586-021-03307-7

Scott, D. C., Rhee, D. Y., Duda, D. M., Kelsall, I. R., Olszewski, J. L., Paulo, J. A., et al. (2016). Two distinct types of E3 ligases work in unison to regulate substrate ubiquitylation. *Cell, 166*(5), 1198–1214. https://doi.org/10.1016/j.cell.2016.07.027

Shire, K., Wong, A. I., Tatham, M. H., Anderson, O. F., Ripsman, D., Gulstene, S., et al. (2016). Identification of RNF168 as a PML nuclear body regulator. *Journal of Cell Science, 129*(3), 580–591. https://doi.org/10.1242/jcs.176446

Sriramachandran, A. M., Meyer-Teschendorf, K., Pabst, S., Ulrich, H. D., Gehring, N. H., Hofmann, K., et al. (2019). Arkadia/RNF111 is a SUMO-targeted ubiquitin ligase with preference for substrates marked with SUMO1-capped SUMO2/3 chain. *Nature Communications, 10*(1), 3678. https://doi.org/10.1038/s41467-019-11549-3

Stingele, J., Bellelli, R., & Boulton, S. J. (2017). Mechanisms of DNA-protein crosslink repair. *Nature Reviews Molecular Cell Biology, 18*(9), 563–573. https://doi.org/10.1038/nrm.2017.56

Streich, F. C., Jr., & Lima, C. D. (2016). Capturing a substrate in an activated RING E3/E2-SUMO complex. *Nature, 536*(7616), 304–308. https://doi.org/10.1038/nature19071

Sun, Y., Chen, J., & Pommier, Y. (2023). Real-time imaging of drug-induced trapping of cellular topoisomerases and poly(ADP-ribose) polymerase 1 at the single-molecule level. *Nucleic Acids Research*. https://doi.org/10.1093/nar/gkad735

Sun, H., & Hunter, T. (2012). Poly-small ubiquitin-like modifier (PolySUMO)-binding proteins identified through a string search. *Journal of Biological Chemistry, 287*(50), 42071–42083. https://doi.org/10.1074/jbc.M112.410985

Sun, H., Leverson, J. D., & Hunter, T. (2007). Conserved function of RNF4 family proteins in eukaryotes: Targeting a ubiquitin ligase to SUMOylated proteins. *The EMBO Journal, 26*(18), 4102–4112. https://doi.org/10.1038/sj.emboj.7601839

Sun, Y., Miller Jenkins, L. M., Su, Y. P., Nitiss, K. C., Nitiss, J. L., & Pommier, Y. (2020). A conserved SUMO pathway repairs topoisomerase DNA-protein cross-links by engaging ubiquitin-mediated proteasomal degradation. *Science Advances, 6*(46). https://doi.org/10.1126/sciadv.aba6290

Swuec, P., Renault, L., Borg, A., Shah, F., Murphy, V. J., van Twest, S., et al. (2017). The FA core complex contains a homo-dimeric catalytic module for the symmetric mono-ubiquitination of FANCI-FANCD2. *Cell Reports, 18*(3), 611–623. https://doi.org/10.1016/j.celrep.2016.11.013

Symington, L. S., & Gautier, J. (2011). Double-strand break end resection and repair pathway choice. *Annual Review of Genetics, 45*, 247–271. https://doi.org/10.1146/annurev-genet-110410-132435

Taglialatela, A., Alvarez, S., Leuzzi, G., Sannino, V., Ranjha, L., Huang, J. W., et al. (2017). Restoration of replication fork stability in BRCA1- and BRCA2-deficient cells by inactivation of SNF2-family fork remodelers. *Molecular Cell, 68*(2), 414–430 e418. https://doi.org/10.1016/j.molcel.2017.09.036

Tarcan, Z., Poovathumkadavil, D., Skagia, A., & Gambus, A. (2022). The p97 segregase cofactor Ubxn7 facilitates replisome disassembly during S-phase. *Journal of Biological Chemistry, 298*(8), Article 102234. https://doi.org/10.1016/j.jbc.2022.102234

Tatham, M. H., Geoffroy, M. C., Shen, L., Plechanovova, A., Hattersley, N., Jaffray, E. G., et al. (2008). RNF4 is a poly-SUMO-specific E3 ubiquitin ligase required for arsenic-induced PML degradation. *Nature Cell Biology, 10*(5), 538–546. https://doi.org/10.1038/ncb1716

Thomas, A., & Pommier, Y. (2019). Targeting topoisomerase I in the era of precision medicine. *Clinical Cancer Research, 25*(22), 6581–6589. https://doi.org/10.1158/1078-0432.CCR-19-1089

Tian, T., Bu, M., Chen, X., Ding, L., Yang, Y., Han, J., et al. (2021). The ZATT-top2a-PICH Axis drives extensive replication fork reversal to promote genome stability. *Molecular Cell, 81*(1), 198–211. https://doi.org/10.1016/j.molcel.2020.11.007

Tian, Y., Liao, F., Wu, G., Chang, D., Yang, Y., Dong, X., et al. (2015). Ubiquitination and regulation of Smad7 in the TGF-beta1/Smad signaling of aristolochic acid nephropathy. *Toxicology Methods, 25*(8), 645–652. https://doi.org/10.3109/15376516.2015.1061082

Uzunova, K., Gottsche, K., Miteva, M., Weisshaar, S. R., Glanemann, C., Schnellhardt, M., et al. (2007). Ubiquitin-dependent proteolytic control of SUMO conjugates. *Journal of Biological Chemistry, 282*(47), 34167–34175. https://doi.org/10.1074/jbc.M706505200

Vancurova, M., Hanzlikova, H., Knoblochova, L., Kosla, J., Majera, D., Mistrik, M., et al. (2019). PML nuclear bodies are recruited to persistent DNA damage lesions in an RNF168-53BP1 dependent manner and contribute to DNA repair. *DNA Repair, 78*, 114–127. https://doi.org/10.1016/j.dnarep.2019.04.001

Vandenberg, C. J., Gergely, F., Ong, C. Y., Pace, P., Mallery, D. L., Hiom, K., & Patel, K. J. (2003). BRCA1-independent ubiquitination of FANCD2. *Molecular Cell, 12*(1), 247–254. https://doi.org/10.1016/s1097-2765(03)00281-8

Vyas, R., Kumar, R., Clermont, F., Helfricht, A., Kalev, P., Sotiropoulou, P., et al. (2013). RNF4 is required for DNA double-strand break repair in vivo. *Cell Death & Differentiation, 20*(3), 490–502. https://doi.org/10.1038/cdd.2012.145

Wagner, K., Kunz, K., Piller, T., Tascher, G., Holper, S., Stehmeier, P., et al. (2019). The SUMO isopeptidase SENP6 functions as a rheostat of chromatin residency in genome maintenance and chromosome dynamics. *Cell Reports, 29*(2), 480–494 e485. https://doi.org/10.1016/j.celrep.2019.08.106

Wang, J., Hu, W., Cai, S., Lee, B., Song, J., & Chen, Y. (2007). The intrinsic affinity between E2 and the Cys domain of E1 in ubiquitin-like modifications. *Molecular Cell, 27*(2), 228–237. https://doi.org/10.1016/j.molcel.2007.05.023

Wang, M., & Pickart, C. M. (2005). Different HECT domain ubiquitin ligases employ distinct mechanisms of polyubiquitin chain synthesis. *The EMBO Journal, 24*(24), 4324–4333. https://doi.org/10.1038/sj.emboj.7600895

Wang, H., Shi, L. Z., Wong, C. C., Han, X., Hwang, P. Y., Truong, L. N., et al. (2013). The interaction of CtIP and Nbs1 connects CDK and ATM to regulate HR-mediated double-strand break repair. *PLoS Genetics, 9*(2), Article e1003277. https://doi.org/10.1371/journal.pgen.1003277

Wang, J., Taherbhoy, A. M., Hunt, H. W., Seyedin, S. N., Miller, D. W., Miller, D. J., et al. (2010). Crystal structure of UBA2(ufd)-ubc9: Insights into E1-E2 interactions in sumo pathways. *PLoS One, 5*(12), Article e15805. https://doi.org/10.1371/journal.pone.0015805

Wang, L., Wansleeben, C., Zhao, S., Miao, P., Paschen, W., & Yang, W. (2014). SUMO2 is essential while SUMO3 is dispensable for mouse embryonic development. *EMBO Reports, 15*(8), 878–885. https://doi.org/10.15252/embr.201438534

Wang, N., Xu, S., & Egli, D. (2023). Replication stress in mammalian embryo development, differentiation, and reprogramming. *Trends in Cell Biology, 33*(10), 872–886. https://doi.org/10.1016/j.tcb.2023.03.015

Weickert, P., & Stingele, J. (2022). DNA-protein crosslinks and their resolution. *Annual Review of Biochemistry, 91*, 157–181. https://doi.org/10.1146/annurev-biochem-032620-105820

Wilson, V. G. (2017). Introduction to sumoylation. *Advances in Experimental Medicine & Biology, 963*, 1–12. https://doi.org/10.1007/978-3-319-50044-7_1

Wu, W., Huang, X. R., You, Y., Xue, L., Wang, X. J., Meng, X., et al. (2021). Latent TGF-beta1 protects against diabetic kidney disease via Arkadia/Smad7 signaling. *International Journal of Biological Sciences, 17*(13), 3583–3594. https://doi.org/10.7150/ijbs.61647

Xiao, Z., Chang, J. G., Hendriks, I. A., Sigurethsson, J. O., Olsen, J. V., & Vertegaal, A. C. (2015). System-wide analysis of SUMOylation dynamics in response to replication stress reveals novel small ubiquitin-like modified target proteins and acceptor lysines relevant for genome stability. *Molecular & Cellular Proteomics, 14*(5), 1419–1434. https://doi.org/10.1074/mcp.O114.044792

Xie, Y., Kerscher, O., Kroetz, M. B., McConchie, H. F., Sung, P., & Hochstrasser, M. (2007). The yeast Hex3.Slx8 heterodimer is a ubiquitin ligase stimulated by substrate sumoylation. *Journal of Biological Chemistry, 282*(47), 34176–34184. https://doi.org/10.1074/jbc.M706025200

Xie, J., Kim, H., Moreau, L. A., Puhalla, S., Garber, J., Al Abo, M., et al. (2015). RNF4-mediated polyubiquitination regulates the Fanconi anemia/BRCA pathway. *Journal of Clinical Investigation, 125*(4), 1523–1532. https://doi.org/10.1172/JCI79325

Xu, Y., Plechanovova, A., Simpson, P., Marchant, J., Leidecker, O., Kraatz, S., et al. (2014). Structural insight into SUMO chain recognition and manipulation by the ubiquitin ligase RNF4. *Nature Communications, 5*, 4217. https://doi.org/10.1038/ncomms5217

Xu, H., Wu, L., Nguyen, H. H., Mesa, K. R., Raghavan, V., Episkopou, V., et al. (2021). Arkadia-SKI/SnoN signaling differentially regulates TGF-beta-induced iTreg and Th17 cell differentiation. *Journal of Experimental Medicine, 218*(11). https://doi.org/10.1084/jem.20210777

Yamamoto, K. N., Kobayashi, S., Tsuda, M., Kurumizaka, H., Takata, M., Kono, K., et al. (2011). Involvement of SLX4 in interstrand cross-link repair is regulated by the Fanconi anemia pathway. *Proceedings of the National Academy of Sciences of the U S A, 108*(16), 6492–6496. https://doi.org/10.1073/pnas.1018487108

Yang, M., Hsu, C. T., Ting, C. Y., Liu, L. F., & Hwang, J. (2006). Assembly of a polymeric chain of SUMO1 on human topoisomerase I in vitro. *Journal of Biological Chemistry, 281*(12), 8264–8274. https://doi.org/10.1074/jbc.M510364200

Yin, Y., Seifert, A., Chua, J. S., Maure, J. F., Golebiowski, F., & Hay, R. T. (2012). SUMO-targeted ubiquitin E3 ligase RNF4 is required for the response of human cells to DNA damage. *Genes & Development, 26*(11), 1196–1208. https://doi.org/10.1101/gad.189274.112

Zhang, F., & Gong, Z. (2021). Regulation of DNA double-strand break repair pathway choice: A new focus on 53BP1. *Journal of Zhejiang University - Science B, 22*(1), 38–46. https://doi.org/10.1631/jzus.B2000306