Coordinate to guard: crosstalk of phosphorylation, sumoylation, and ubiquitylation in DNA damage response

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Small ubiquitin-like modifier-1/2/3 (SUMO-1/2/3) and ubiquitin share similar structure and utilize analogous machinery for protein lysine conjugation. Although sumoylation and ubiquitylation have distinct functions, they are often tightly associated with each other to fine-tune protein fate in transducing signals to regulate a wide variety of cellular functions, including DNA damage response, cell proliferation, DNA replication, embryonic development, and cell differentiation. In this Perspective, we specifically highlight the role of sumoylation and ubiquitylation in ataxia-telangiectasia mutated (ATM) signaling in response to DNA double-strand breaks and hypothesize that ATM-induced phosphorylation is a unique node in regulating SUMO-targeted ubiquitylation in mammalian cells to combat DNA damage and to maintain genome integrity. A potential role for the coordination of these three types of post-translational modification in dictating the tempo and extent of cellular response to genotoxic stress is speculated.

Keywords: ATM, phosphorylation, sumoylation, ubiquitylation, DNA damage response

Sumoylation regulates ATM-mediated DNA damage signaling in both transcription and chromatin remodeling. A unique example that well-illustrates the relationship between ATM-induced phosphorylation and sumoylation is Krüppel-associated box (KRAB)-associated protein 1 (KAP1; also known as TRIM28 and TIF1β)). KAP1 is a transcriptional co-repressor primarily responding to DNA damage and regulating cellular functions such as checkpoint control and apoptosis. KAP1 has six putative sumoylation sites and its sumoylation at Lys-779 and Lys-804 are required for the interaction with chromatin remodelers including heterochromatin protein 1 (HP1), SET domain, bifurcated 1 (SETDB1), nucleosome remodeling deacetylase (NuRD), and histone deacetylases (HDACs) to establish a silent state of
ATM-induced phosphorylation inhibits negative regulators of p53, A TM also represses transcription in the case of the tumor suppressor p53, A TM-induced phosphorylation participates in the dual function of repressing and promoting the ubiquitylation of different effectors, leading to their degradation. p53 induces transcription of multiple genes important for cell cycle regulation, DNA repair, and apoptosis. A TM phosphorylates p53 at Ser-15, leading to transcription of the CDK2/cyclin-E inhibitor which functions at the G1-S checkpoint (Shiloh, 2003). ATM-induced phosphorylation inhibits negative regulators of p53, including MDM2 and constitutive morphogenic 1 (COP1). Both MDM2 and COP1 are Ub E3 ligases that ubiquitylate p53 to promote its proteasomal degradation. ATM indirectly regulates MDM2-mediated degradation of p53 through phosphorylation of Chk2 which then phosphorylates p53 at Ser-20 to prevent the formation of the MDM2–p53 complex (Dumaz et al., 2001). ATM also directly phosphorylates MDM2 at Ser-395 to prevent the export of the MDM2–p53 complex into the cytoplasm, thereby maintaining p53 in the nucleus (Maya et al., 2001; Chen et al., 2005). In addition, phosphorylation of COP1 by ATM induces autoubiquitylation of COP1 (Dornan et al., 2006). ATM phosphorylation thus selectively influences the repression and activation of ubiquitylation on different proteins in response to DNA damage. Taken together, ATM-induced phosphorylation in coordination with ubiquitylation plays an essential role in establishing a series of signals directing to transcriptional regulation, the completion of DSB repair and in determining the fate of key proteins involved in DDR.

CROSSTALK BETWEEN SUMOYLATION AND UBQITYLATION IN DDR

The convergence of sumoylation and ubiquitylation does take place under genotoxic condition. When DSBs occur, protein inhibitor of activated signal transducer and activator of transcription (PIAS) localizes to the damage sites. PIAS1 and PIAS4 function as SUMO E3 ligase to modify BRCA1, 53BP1 and possibly repairing the damage, the removal of H2AX from the damage sites involves an acetylation-dependent ubiquitylation catalyzed by TIP60–UBC13 complex (Ikura et al., 2007).

Other than transducing signals to recruit repair proteins, ATM also represses transcription in cis to DSBs by establishing monoubiquitylation of H2A to inhibit RNA polymerase II function. Since monoubiquitylation at Lys-119 of H2A (uH2A) is associated with transcriptional repression, ATM-mediated transcriptional silencing was explored in tandem with uH2A. By inhibiting ATM, uH2A levels at DSBs are significantly decreased although the Lys-63-linked poly Ub chains and RAP80 levels around the foci are less affected. ATM therefore plays a critical role in maintenance of uH2A at DSBs through RNF8/RNF168, while the Lys-63-linked poly Ub chains serve as separate docking sites for recruitment of repair proteins such as BRCA1 complex. Furthermore, ATM-dependent uH2A stalls RNA polymerase II-mediated transcription in cis to the damage site. A debiquitylation enzyme, USP16, negatively regulates uH2A-dependent function and rapidly restores transcription after the cessation of DNA damage (Shanbhag et al., 2010).

Ataxia-telangiectasia mutated-induced phosphorylation also exhibits crosstalk with ubiquitylation by mediating protein degragation through direct and indirect recruitment of Ub E3 ligases. In the case of the tumor suppressor p53, ATM-induced phosphorylation participates in the dual function of repressing and promoting the ubiquitylation of different effectors, leading to their degradation. p53 induces transcription of multiple genes important for cell cycle regulation, DNA repair, and apoptosis. A TM phosphorylates p53 at Ser-15, leading to transcription of the CDK2/cyclin-E inhibitor which functions at the G1-S checkpoint (Shiloh, 2003). ATM-induced phosphorylation inhibits negative regulators of p53, including MDM2 and constitutive morphogenic 1 (COP1). Both MDM2 and COP1 are Ub E3 ligases that ubiquitylate p53 to promote its proteasomal degradation. ATM indirectly regulates MDM2-mediated degradation of p53 through phosphorylation of Chk2 which then phosphorylates p53 at Ser-20 to prevent the formation of the MDM2–p53 complex (Dumaz et al., 2001). ATM also directly phosphorylates MDM2 at Ser-395 to prevent the export of the MDM2–p53 complex into the cytoplasm, thereby maintaining p53 in the nucleus (Maya et al., 2001; Chen et al., 2005). In addition, phosphorylation of COP1 by ATM induces autoubiquitylation of COP1 (Dornan et al., 2006). ATM phosphorylation thus selectively influences the repression and activation of ubiquitylation on different proteins in response to DNA damage. Taken together, ATM-induced phosphorylation in coordination with ubiquitylation plays an essential role in establishing a series of signals directing to transcriptional regulation, the completion of DSB repair and in determining the fate of key proteins involved in DDR.

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RNF8, RNF168 to modulate their activities in facilitating Ub signal amplification and DNA repair after genotoxic stress (Galanty et al., 2009). Sumoylation on BRCA1 increases its Ub E3 ligase activity, therefore termed as a SUMO-regulated Ub ligase (SRUbL; Morris et al., 2009). It is still not clear how PIAS activity is regulated under DNA damage condition, and whether this is dependent on ATM-induced phosphorylation. PIAS1 is phosphorylated by IκB kinase alpha (IKKα; Liu et al., 2007), whose activity is also regulated by ATM-dependent NF-κB essential modulator (NEMO) ubiquitylation (Wuerzberger-Davis et al., 2006), implying that the role of PIAS in DDR might also be incorporated into ATM signaling.

Another interesting example showing the interplay between sumoylation and ubiquitylation in the context of genotoxic stress is SUMO-targeted ubiquitin ligase (STUbL), including Slx8–Rfp, MIP1, Slx5–Slx8, and RNF4. It is a new class of ubiquitin E3 ligases targeting sumoylated proteins through their SIMs for ubiquitylation. STUbL has been reported to trigger the degradation of sumoylated proteins and is responsible for the maintenance of cell survival and genome stability (Lallemand-Breitenbach et al., 2008; Tatham et al., 2008; Cook et al., 2009; Heideker et al., 2009). For example, RNF4 (RING finger protein 4, RING: Really Interesting New Gene), the only human homolog of Slx8–Rfp, is involved in arsenic-trioxide (ATO)-induced polyubiquitylation and proteasomal degradation of promyelocytic leukemia (PML) by targeting the poly SUMO-2 chain on PML (Lallemand-Breitenbach et al., 2008; Tatham et al., 2008). This reveals the role of RNF4 in mediating the crosstalk between sumoylation and ubiquitylation and also provides a possible mechanism of ATO-induced damage response.

In conclusion, crosstalk between sumoylation and ubiquitylation seems like a general scenario in DDR; however, it is still not fully understood how this crosstalk might be modulated and since ATM signaling requires sumoylation and ubiquitylation to respond to DSB, it is possible that ATM is involved in tuning SUMO–Ub crosstalk through RNF4 in DDR.

**IS RNF4 INVOLVED IN ATM SIGNALING?**

Given to the fact that RNF4 biologically functions as an important factor for maintaining genome integrity and its ability to recognize and possibly regulate more than 300 substrates involved in a wide variety of biological processes, including chromatin remodeling and DNA repair etc. Bruderer et al. (2011), one could speculate that RNF4 might participate in ATM-regulated DSB damage response.

**RNF4 IS EXTENSIVELY INVOLVED IN DNA DAMAGE SIGNALING PATHWAYS**

Yeast homolog of RNF4, Slx5/Slx8 physically associates with DSBs to form damage foci, in a SUMO and SIM-dependent way (Nagai et al., 2008; Cook et al., 2009). Slx8 functions with Rad60, a DNA repair protein, and Nse2, a SUMO ligase to protect the genome from Topoisomerase-1 (Top-1)-induced DNA damage (Prudden et al., 2000).

![FIGURE 1](https://www.frontiersin.org) Sequence alignment of SIMs and ARR of RNF4 family members from different organisms. Data here show that four SIM domains and ARR are conserved throughout evolution.
Fission yeast Rfp1 and Rfp2 complement one another in regulating defects in cell cycle progression and Chk1-dependent DNA repair; moreover, human RNF4 is able to functionally rescue this phenotype in rfp1/rfp2 double null mutant (Kosoy et al., 2007). RNF4 also functions specifically to demethylate DNA by interacting with base excision repair enzymes TDG and APE1 that target G:T mismatches in the DNA. In addition, RNF4 deficiency displays global DNA hypermethylation (Hu et al., 2010). Taken together, the biological function of RNF4 is conserved and tightly associated with DDR, especially DNA repair and chromatin remodeling in different organisms, supporting the idea that RNF4 plays a role in coordinating and transducing ATM-induced signaling in response to DNA damage.

EVIDENCE SUPPORTING PHOSPHORYLATION-INDUCED SUMO-DEPENDENT PROTEIN DEGRADATION
Promyelocytic leukemia is found to be degraded upon ATO-treatment and the degradation is dependent on the phosphorylation-induced by ATO and the subsequent increase of sumoylation (Lallemand-Breitenbach et al., 2001; Hayakawa and Privalsky, 2004). ATO-induced sumoylation on Lys-160 is critical for recruiting RNF4 to ubiquitylate PML for proteasomal degradation (Lallemand-Breitenbach et al., 2001; Petrie and Zelent, 2008). Although there is no direct link showing phosphorylation of PML promotes SUMO-dependent degradation, either phosphorylation-defective, or sumoylation-defective PML mutant shows abolished downstream effects in response to ATO-treatment (Lallemand-Breitenbach et al., 2001, 2008), implying that both modifications and their crosstalk are indispensable in leading to ATO-induced PML degradation. PML can be phosphorylated by several kinases including MAPK, CK2, and CHK2 (Yang et al., 2002; Hayakawa and Privalsky, 2004; Joe et al., 2006; Scaglioni et al., 2006). Interestingly, phosphorylation-defective PML is stabilized upon DNA damage triggered by γ-irradiation and results in decreased apoptotic activity, in an ATM/CHK2-dependent manner (Yang et al., 2002). Evidence from the PML studies provide some hints supporting that the degradation promoted by RNF4 is possibly regulated by phosphorylation; however, it is still unclear how phosphorylation induces sumoylation of PML and whether there is another mechanism that phosphorylation of PML might enhance the recognition by RNF4.

UNIQUE STRUCTURAL CHARACTERISTIC OF RNF4 POSSIBLY LINKS PHOSPHORYLATION, SUMOYLATION AND UBIQUITYLATION
If one speculates that RNF4-mediated SUMO-targeted ubiquitylation is regulated by ATM-induced phosphorylation, what would the mode of regulation be? A unique region is found in RNF4 protein. Following the four SIMs, there is a region rich with arginine, named arginine-rich region (ARR) in RNF4 (Figure 1), denoting that this region provides positive charge to attract phosphorylated protein with negative charge. The electrostatic interaction between arginine and phosphate forms a covalent-like binding (Woods and Ferre, 2005). Thus, the ARR in RNF4 might enhance its interaction with target proteins phosphorylated by ATM. In summary, phosphorylation on RNF4 target proteins might be a mode to regulate RNF4-mediated, SUMO-targeted ubiquitylation and related biological function.

A POTENTIAL MECHANISM OF RNF4 TARGETING ATM SUBSTRATES FOR PROTEASOMAL DEGRADATION
It was noted that phosphorylation and subsequent sumoylation of PML occur within 1 h after treating with ATO (Lallemand-Breitenbach et al., 2001; Hayakawa and Privalsky, 2004); however, significant degradation of PML is observed around 12–16 h after ATO-treatment (Lallemand-Breitenbach et al., 2001, 2008), indicating that the regulation of RNF4-mediated PML degradation might be in slow kinetics. This suggests that there might be other factors required for targeting RNF4-ubiquitylated PML to proteasomal degradation for degradation.
proteasome. An AAA-ATPase p97, its adaptors UFD1 and NPL4 are implicated in recognizing and extracting polyubiquitylated proteins to proteasome for degradation in various cellular context, including mitosis, DNA replication, and DNA damage (Richly et al., 2005; Ramadan et al., 2007; Mouysset et al., 2008; Meerang et al., 2011; Verma et al., 2011). To explain the observation of slow degradation of PML, rather than rapid turnover, in our view, RNF4 may serve as a signal transducer that senses SUMO signal and amplifies Ub signal on its substrates to recruit selective cargo proteins, such as p97–UFD1–NPL4 complex to extract the ubiquitylated substrates for proteasomal degradation.

CONCLUSION AND PERSPECTIVE
Sumoylation and ubiquitylation widely participate in ATM-regulated DDR. When cells are exposed to genotoxic stress, DSBRs activate ATM to phosphorylate a subset of target proteins to transduce signals and to induce checkpoint control and DNA repair machinery. This process largely involves the cooperation of sumoylation and ubiquitylation to regulate cellular function in response to DSB. However, little is known about the detailed mechanism of SUMO–Ub crosstalk. Here, we hypothesize that RNF4 plays a central role in recognizing ATM-induced phosphorylation and sumoylation to provide an additional Ub signal to recruit Ub-selective segregrate to target for proteasomal degradation (Figure 2). This provides a novel view on the crosstalk among multiple PTMs. The crosstalk of phosphorylation, sumoylation, and ubiquitylation denotes a cooperative network in protecting cells from DNA damage and maintaining genome integrity. Defects in this network may lead to genome instability and consequently tumorigenesis. Moreover, modulation of the players involved in the network may sensitize cancer cells to DNA damage-based cancer therapy and benefit the patients.

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