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REVIEW ARTICLE

Regulation of DNA damage-induced ATM activation by histone modifications

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Abstract

Ataxia-telangiectasia mutated (ATM) is an apical kinase involved in the cellular response to DNA damage in eukaryotes, especially DNA double-strand breaks (DSBs). Upon DSB, ATM is activated through a hierarchy of well-organized cellular processes and machineries, including post-translational modifications (PTMs), the MRE11-RAD50-NBS1 (MRN) complex and chromatin perturbations. ATM activation initiates a cascade of chromatin modifications and nucleosome remodeling that permits the assembly of repair factors that ensure a highly orchestrated response to repair damaged DNA. Numerous studies have tried to elucidate the mechanisms of ATM activation, but how it is activated by DNA damage signals is still unclear. Histone modifications are considered essential for regulating ATM activation: a histone octamer constitutes the nucleosome core and histone tails protrude into the DNA strands to alter the chromatin landscape and DNA accessibility. Here, we summarize how histone modifications regulate ATM activation, with an emphasis on the functional relevance in DNA damage response and repair.

Keywords ATM activation · Histone modification · DNA damage response · DNA repair

Introduction

Genome stability and integrity are constantly challenged by exogenous insults (irradiation, UV, chemical regents, etc.) and endogenous damage (metabolic wastes, replication stress, etc.), which lead to DNA damage and may alter the genetic information if left unrepaired. DNA double-strand breaks (DSBs), in which both strands of the DNA duplex are broken, are the most dangerous and deleterious form of DNA damage. DSB repair requires a massive complicated machinery that involves hundreds of proteins that survey mega bases (Mb) of DNA sequence around and flanking the DSB site. In eukaryotic cells, DSBs are mainly repaired through two pathways: non-homologous end joining (NHEJ) and homologous recombination (HR). The pathway type is chosen depending on genomic location of the DSB, cell-cycle stage and genetic background (Sancar et al. 2004). Deficiencies in responding and repairing DSBs have been linked to various human disorders, including cancer (Jackson and Bartek 2009). Uncovering the nature of the DSB response and repair, therefore, is informative for disease prevention and intervention.

Among the hierarchical events in response to DNA DSBs, activation of Ataxia-telangiectasia mutated (ATM) is considered the most critical. ATM deletion or mutation leads to near-complete loss of response to DSBs, as evident in patients with Ataxia-telangiectasia (A-T) and ATM-deficient cells (Savitsky et al. 1995; Barlow et al. 1996; Elson et al. 1996; Xu et al. 1996). Failure to robustly activate ATM also results in an inadequate DNA damage response and thus inappropriate repair of DSBs, even if ATM is genetically intact and functional. This scenario is evident in various genetic disorders, such as Nijmegen Breakage Syndrome (NBS), caused by mutation or deletion of NBS1 (Carney et al. 1998; Varon et al. 1998). As a protein serine/threonine kinase, ATM was first recognized as a key regulator of the DNA damage response when it was linked to *A–T*, which displays hypersensitivity to irradiation and cancer predisposition. Since then, ATM has been demonstrated

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to regulate the DNA damage response and DNA repair by phosphorylating various substrates, including p53, histone H2AX, checkpoint kinase 2 (CHK2) (Banin et al. 1998; Canman et al. 1998; Rogakou et al. 1998; Burma et al. 2001; Matsuoka et al. 1998, 2000). Mechanistically, ATM facilitates DSB repair factor loading in three main ways: (i) by creating a platform to recruit and assemble repair factors, (ii) by changing nucleosome accessibility by altering local chromatin states, and (iii) by promoting histone exchange through chromatin remodeling (Sirbu and Cortez 2013). For example, ATM-mediated H2AX phosphorylation at serine 139 (also termed γH2AX) recruits mediator of checkpoint 1 (MDC1), which in turn recruits ATM through a positive feedback loop to amplify ATM signals (Stucki and Jackson 2006). The γH2AX/MDC1 platform also recruits downstream chromatin modifiers, such as the ubiquitin E3 ligases RNF8/168 to foster sequential loading of repair factors (Stucki and Jackson 2006; Mailand et al. 2007; Huen et al. 2007; Kolas et al. 2007).

The mechanisms underlying ATM activation remained obscure until it was demonstrated that ATM autophosphorylation at its serine 1981 residue (S1981) was essential (Bakkenist and Kastan 2003). ATM homodimers or multimers in quiescent cells are disrupted into monomers by DNA damage-induced intermolecular phosphorylation, which was later proved to take place at multiple sites and not just S1981 alone (Bakkenist and Kastan 2003; Pellegrini et al. 2006; Kozlov et al. 2006; Daniel et al. 2008; (Kozlov et al. 2011). ATM phosphorylation by other kinases, such as cyclin-dependent kinase 5 (CDK5) and DNA-dependent protein kinase (DNA-PK), is also important for ATM activation (Tian et al. 2009; Zhou et al. 2017). Other post-translational modifications (PTMs), including acetyltransferase TIP60-mediated acetylation and protein phosphatase 2A/2C (PP2A/2C)-mediated dephosphorylation are also crucial ATM regulators (Sun et al. 2005; Goodarzi et al. 2004; Shreeram et al. 2006). The MRE11-RAD50-NBS1 (MRN) complex is another indispensable cellular component in regulating ATM activity. Early observations in patients with NBS and Ataxia-telangiectasia like disease (ATLD) that is caused by MRE11 mutation or deletion, documented a marked similarity in patient phenotypes to patients with A-T, including radio-sensitivity and cancer predisposition (Carney et al. 1998; Varon et al. 1998; Stewart et al. 1999). Later studies revealed that MRN complex functions as the main damage sensor upstream of ATM signaling (Carson et al. 2003). It was further confirmed that MRN is required for both initial and robust ATM activation in vivo and in vitro, by promoting ATM monomerization, recruitment to damage sites and interaction with its substrates (Uziel et al. 2003; Lee and Paull 2004; Difilippantonio et al. 2005; Lee and Paull 2005; Dupre et al. 2006; Falck et al. 2005). Moreover, nuclease activity of MRE11 is also required for ATM activation, probably through generation of ssDNA oligos when processing DNA breaks (Dupre et al. 2008; Jazayeri et al. 2008). In vivo activation of ATM indeed depends on the presence of DNA, as dimeric ATM cannot be activated or autophosphorylated when DNA is absent (Lee and Paull 2005; Dupre et al. 2006). Despite DNA damage-induced ATM activation being regulated by the above-mentioned mechanisms, ATM activation under other circumstances may not necessarily need any of them. For example, oxidative stress activates ATM by forming an intermolecular disulfide bond at cysteine 2991 residue (C2991), which is independent of autophosphorylation or MRN (Guo et al. 2010). In addition, ATM interacting protein (ATMIN) mediates ATM activation upon hypotonic stress through a MRN-independent pathway (Kanu and Behrens 2007).

Chromatin alterations may also participate in regulating ATM activation, as Bakkenist CJ et al. first reported that non-DNA damaging stimuli, such as histone deacetylase (HDAC) inhibitors and sodium chloride, could also potently activate ATM, even without eliciting any DNA breaks (Bakkenist and Kastan 2003). Since this discovery, it was anticipated that chromatin may sense initial DNA damage signals and transduce these signals to ATM through chromatin alterations or modifications. Later studies proved this theory by showing that chromatin modifications, including certain types of histone modifications, are mechanistically and functionally relevant to ATM activation. This finding is expected and rational, as histones are so tightly linked to DNA that histone modifications are known to impact almost all DNA properties and functions, such as replication and transcription. Consequently, histone modifications have also been extensively explored in terms of how they regulate the DNA damage response and DNA repair (Cao et al. 2016). The complexity of histone modifications adds another layer of regulation so that the DNA damage response and repair machinery can be loaded to damaged chromatin in a precise and orchestrated manner. In this review, we detail the mechanisms as to how histone modifications regulate ATM activation. We elaborate the implications of these modifications on the DNA damage response and repair, as well as other cellular functions.

Histone phosphorylation

One of the best-characterized histone modifications involved in ATM activation is γH2AX (Fig. 1), which is among the first substrates phosphorylated by ATM upon DNA damage (Rogakou et al. 1998; Burma et al. 2001). As a variant of the core histone H2A, H2AX comprises ~ 10% of the total H2A in the eukaryotic genome (Fernandez-Capetillo et al. 2004), suggesting that only one in 10 nucleosomes contains H2AX. H2AX phosphorylation occurs at DNA damage

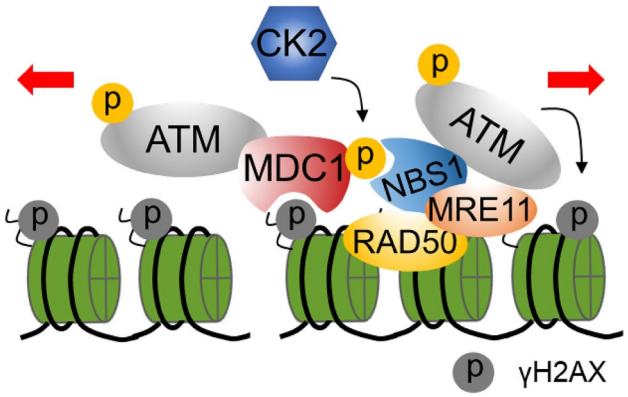

Fig. 1 Regulation of ATM activation by γH2AX. ATM is recruited to DSB sites by MRN complex and activated. The phosphorylation of H2AX (γH2AX) by ATM is recognized by the BRCT domain of MDC1 and the phosphorylation of MDC1 by CK2 is recognized by NBS1 component of MRN complex. This promotes the recruitment of another MRN complex, which in turn recruits and activates more ATM molecules for another cycle. This positive feedback loop leads to the spreading of DNA damage-induced ATM signaling along the DSB-flanking chromatin, thus promoting the robust and full ATM activation

sites within a few seconds and spreads over 1 Mb flanking regions (Rogakou et al. 1998), indicating that H2AX undergoes rapid exchange and re-localization in response to DNA damage. H2AX-deficient mice display various DNA-damage-associated phenotypes, including increased sensitivity to radiation, chromosome instability, growth retardation, immune deficiency, and infertility (Celeste et al. 2002, 2003). These phenotypes are largely shared by ATM-deficient mice and A–T patients (Savitsky et al. 1995; Barlow et al. 1996; Elson et al. 1996; Xu et al. 1996), suggesting a critical role for H2AX in the ATM pathway. In addition, H2AX S139 mutation specifically sensitizes mice or cells to DNA DSBs (Celeste et al. 2003).

Although γH2AX is dispensable for initially recognizing DNA breaks (Celeste et al. 2003), it amplifies ATM-dependent phosphorylation signals through a positive feedback loop. Mechanistically, γH2AX recruits MDC1 via a direct interaction with its breast cancer C-terminal (BRCT) domain (Stucki et al. 2005; Lou et al. 2006). MDC1 phosphorylation by casein kinase 2 (CK2) is then recognized by NBS1 and promotes MRN complex recruitment and retention, which in turn recruits and activates ATM. This process leads to the stabilization and amplification of DNA damage-induced phosphorylation signals (Spycher et al. 2008; Melander et al. 2008; Wu et al. 2008; Chapman and Jackson 2008). Despite the established role of H2AX phosphorylation in ATM activation, a H2A variant found in *Arabidopsis* (H2A.W.7) is primarily confined to heterochromatin, and is also phosphorylated by ATM and required for an ATM-dependent DNA damage response in heterochromatic regions (Lorkovic et al. 2017). Moreover, H2AX phosphorylation at tyrosine 142 (T142), which is regulated by the WSTF kinase and rapidly dephosphorylated by EYA protein phosphatase upon DNA damage, is also critical for an ATM-dependent DNA damage response (Xiao et al. 2009; Cook et al. 2009; Krishnan et al. 2009). H2AX phosphorylation at S139 and T142 coordinates the DNA damage response by recruiting Microcephalin (MCPH1) (Singh et al. 2012), suggesting a crosstalk between these H2AX phosphorylation events.

In addition to H2A and its variants, phosphorylation of other histones is also involved in ATM signaling. For example, in budding yeast, histone H2B is phosphorylated at threonine 129 (T129) in a Mec1 (yeast homolog of ATR)-dependent and Tel1 (yeast homolog of ATM)-dependent manner (Lee et al. 2014). H2B phosphorylation shows a similar pattern to γH2AX, despite differences in telomeric regions (Lee et al. 2014), suggesting that H2B phosphorylation may also be an active regulator of the DNA damage response. Early studies showed that histone H1 and H3 are instantaneously dephosphorylated upon DNA damage, whereas H1 dephosphorylation is dependent on ATM (Guo et al. 1999, 2000). Although direct evidence is still lacking, these dynamic modifications may have an indirect influence on the DNA damage response. H3 serine 10 (S10) dephosphorylation in G1 phase correlates with γH2AX upon DNA damage (Sharma et al. 2015, 2015). As H3S10 phosphorylation is critical in chromatin condensation (Johansen and Johansen 2006), these data suggest its potential involvement in ATM activation during cell-cycle progression. In addition, H3 phosphorylation at threonine 11 (T11) by checkpoint kinase 1 (CHK1) is also a DNA damage responsive phosphor-mark and DNA damage induces rapid dephosphorylation of H3T11 by protein phosphatase 1γ (PP1γ) (Shimada et al. 2008, 2010). H3T11 phosphorylation is prevented by H3S10 phosphorylation through an intramolecular autoinhibitory feedback mechanism (Liokatis et al. 2012), indicating a dual role for H3S10 phosphorylation in the DNA damage response.

Histone methylation

Chromatin is marked at multiple sites by histone methylation, which carries distinct epigenetic information and coordinates a wide range of cellular functions. Histone methylation is regulated by a group of lysine methyltransferases (KMTs) and demethylases (KDMs), which have a high specificity to target different lysine residues. Various histone methylation sites are dynamically altered, either globally or locally upon DNA damage (Chen and Zhu 2016). One of the key histone methylation sites involved in ATM signaling is H3 lysine 9 (H3K9) (Fig. 2), which is initially identified as an essential factor in gene repression and heterochromatin

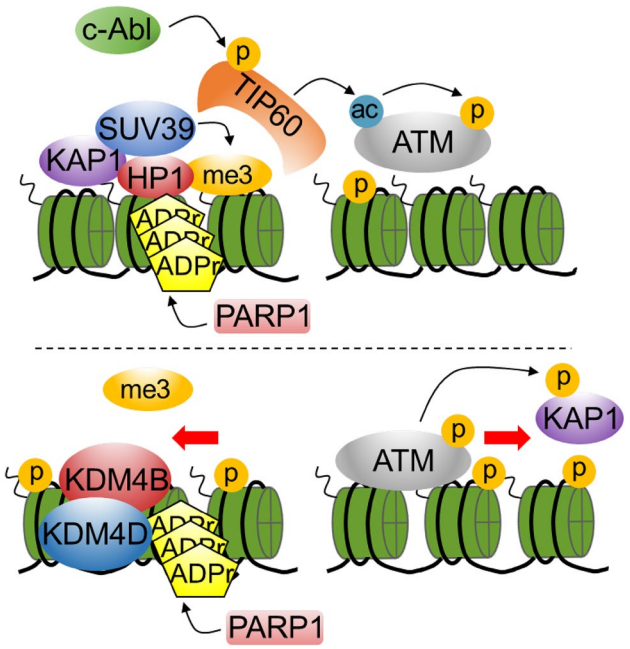

Fig. 2 Regulation of ATM activation by H3K9 trimethylation. In response to DNA damage, KAP1/HP1/SUV39H1 complex is recruited to DSB sites by PARP1-dependent chromatin PARylation. SUV39H1 catalyzes H3K9me3, which recruits more SUV39H1 complex through interaction with HP1, thus promoting H3K9me3 spreading in a positive feedback loop. The H3K9me3 activates TIP60 HAT activity and TIP60 phosphorylation by c-Abl promotes its interaction with H3K9me3. The activated TIP60 then promotes ATM activation through acetylation-dependent autophosphorylation. The activated ATM further promotes KAP1 phosphorylation and disassociation from chromatin, and KDM4B/D recruited by chromatin PARylation promotes the demethylation of H3K9, indicating the highly dynamic behaviour of H3K9me3 in ATM orderly activation

formation. H3K9 trimethylation (H3K9me3) recruits a repressive complex containing heterochromatin protein 1 (HP1) (Bannister et al. 2001; Nielsen et al. 2001; Lachner et al. 2001; Nielsen et al. 2002; Jacobs and Khorasanizadeh 2002), whereas loss of H3K9me3 or its enzymes results in chromatin relaxation and genome instability (Peng and Karpen 2009; Wang et al. 2013). In response to DNA damage, SUV39H1, a major KMT for H3K9me3, is recruited to DSB sites by chromatin poly-ADP-ribosylation (PARylation), which promotes chromatin compaction through H3K9me3 and the KAP1/HP1/SUV39H1 complex (Ayrapetov et al. 2014). TIP60, which is recruited by MRN in the form of ATM-FOXO3a-TIP60 complex (Tsai et al. 2008; Sun et al. 2009; Adamowicz et al. 2016), is then activated by H3K9me3 via its chromodomain and activates ATM by acetylating lysine 3016 (K3016) (Sun et al. 2005, 2009). These studies demonstrate that H3K9me3 and transient chromatin condensation is required for ATM activation. Nevertheless, chromatin needs to be open to facilitate the expansion of DNA damage signals to distal regions and the recruitment of downstream repair factors. After the initial wave of DNA damage sensing and transducing, activated ATM phosphorylates KAP1 and removes the KAP1/HP1/SUV39H1 complex (Ayrapetov et al. 2014; Ziv et al. 2006), which forms a negative feedback loop to achieve ATM-dependent chromatin decompaction. In addition, KDM4B and KDM4D, which are responsible for demethylating H3K9me2/3, are recruited to DNA damage sites in a PARP1-dependent manner (Young et al. 2013; Khoury-Haddad et al. 2014), indicating an active demethylation of H3K9me2/3 after ATM activation. More importantly, KDM4D is required for efficient ATM activation and recruitment (Khoury-Haddad et al. 2014), and oncogenic stress induced heterochromatin retains DDR signaling (Di Micco et al. 2011), further suggesting that dynamic H3K9 methylation and demethylation are indispensable for timely and orderly ATM activation.

H3 lysine 36 (H3K36) methylation is another important histone mark that has been linked to ATM activation. H3K36 dimethylation (H3K36me2) is induced at DNA damage sites and potentiates NBS1 and Ku70 recruitment; K36 mutation impairs the enrichment of these factors and compromises DSB repair (Fnu et al. 2011; Cao et al. 2016). As NBS1 is a key component of the ATM regulatory machinery, it is expected that H3K36me2 may modulate ATM activation. Indeed, we showed that KDM2A, the major KDM for H3K36me2, is phosphorylated by ATM and displaced from DSBs. This process promotes H3K36me2 and MRN complex recruitment, forming a positive feedback loop to achieve robust ATM activation (Cao et al. 2016). Contrary to H3K36me2, H3K36 trimethylation (H3K36me3) is not induced by DNA damage, yet it is still actively involved in the DNA damage response and DNA repair. Depletion or mutation of SETD2, a major H3K36me3 KMT, diminishes ATM activation, p53-mediated checkpoint activation, loading of HR factors and DSB repair (Pfister et al. 2014; Carvalho et al. 2014; Jha and Strahl 2014). H3K36me3 also recruits several readers that may be implicated in ATM activation. For example, plant homeodomain finger protein 1 (PHF1) recruitment via an interaction between its Tudor domain and H3K36me3 is required for its loading onto DNA damage sites (Hong et al. 2008; Musselman et al. 2012). The fact that PHF1 is involved in DNA damage repair and increases nucleosome accessibility raises the possibility that H3K36me3 may direct ATM signaling via PHF1 (Hong et al. 2008; Musselman et al. 2013). Moreover, crosstalk between H3K36me3 and H4K16 acetylation results in TIP60 recruitment through lens epithelium-derived growth factor p75 splicing variant (LEDGF), an H3K36me3 reader (Li and Wang 2017). The established role of TIP60 in ATM activation also prompts us to speculate a more direct link between H3K36me3 and ATM activation.

Beside H3K9 and H3K36 methylation, many other histone sites that are methylated are also potential modulators

of the DNA damage response and ATM activation. For example, H4K20 methylation is induced by MMSET in an ATM-dependent manner, which is important for loading p53-binding protein 1 (53BP1), a key factor involved in DSB repair (Pei et al. 2011). Recent data showed that DSB-induced small RNAs (diRNAs)-dependent recruitment of MMSET and TIP60 potentiates a more flexible chromatin through H4K20 methylation and H4K16 acetylation (Wang and Goldstein 2016). MMSET and H4K20 methylation, however, does not affect ATM-dependent γH2AX formation in these settings (Pei et al. 2011; Wang and Goldstein 2016), suggesting a specific role of H4K20 methylation in the DNA damage response. A similar methylation site is H3 lysine 79 (H3K79), which is not induced by DNA damage, but is required for 53BP1 recruitment (Huyen et al. 2004; Giannattasio et al. 2005; Wysocki et al. 2005). The fact that 53BP1 interacts with the MRN complex and can promote MRN-dependent ATM activation (Lee et al. 2010), however, indicates a possible feedback loop between these histone modifications and ATM signaling through 53BP1. DNA damage induces accumulation of H3K27 trimethylation (H3K27me3) and enhancer of zeste homolog 2 (EZH2), the KMT for H3K27me3, via a PARP1-dependent pathway (Chou et al. 2010). In addition, as EZH2 regulates the cellular response to different DNA damage inducers, its deletion sensitizes cells to DNA damage (Wu et al. 2011; Sha et al. 2016). Moreover, ATM regulates EZH2 stability through phosphorylation, and ATM deficiency leads to elevated H3K27me3 levels in A–T neural cells (Li et al. 2013). Whereas H3K27me3 patterns correlate with deregulated neural genes in A–T brains, EZH2 knockdown rescues the neurological abnormalities (Li et al. 2013), suggesting a direct role for EZH2 and H3K27me3 in ATM function in the neural system. A recent study further confirmed that EZH2 regulates ATM activation and its subsequent involvement in lipid metabolism and the DNA damage response in glioblastoma (Ahmad et al. 2017).

Histone acetylation

Histone acetylation is dynamically balanced by histone acetyltransferases (HATs) and HDACs. While some HDAC inhibitors have been approved to treat certain types of malignancies (Li and Zhu 2014), they are also DNA damage inducers and regulators (Namdar et al. 2010; Lee et al. 2010; Robert et al. 2011; Wang et al. 2012). The observation that HDAC inhibitors can potently activate ATM leads to the presumption that histone acetylation may also be a *bona fide* regulator of ATM activation (Bakkenist and Kastan 2003). Different from the mechanisms employed by histone phosphorylation and methylation, which act through the recruitment of specific readers, histone acetylation mainly alters local chromatin states and accessibility to connect chromatin alterations and ATM activation. Kim YC et al. first demonstrated that the nucleosome-binding protein high mobility group N1 (HMGN1) optimizes ATM activation by regulating its interaction with chromatin through histone H3 at lysine 14 (H3K14) acetylation (Kim et al. 2009). The researchers found that exposing cells to an HDAC inhibitor upregulated H3K14 acetylation and bypassed the requirement of HMGN1 for efficient ATM activation (Kim et al. 2009). These data suggest that H3K14 acetylation may regulate ATM chromatin retention and activation.

Another important histone acetylation mark associated with ATM activation is acetylation of histone H4 at lysine 16 (H4K16). H4K16 acetylation is a predominant factor controlling chromatin structure and nucleosome mobilization (Shogren-Knaak et al. 2006), and is required for ATM activation. Depletion of the acetyltransferases responsible for H4K16 acetylation, including MOF and TIP60, leads to profound defects in ATM activation and the DNA damage response (Sun et al. 2005; Gupta et al. 2005; Sharma et al. 2010). TIP60 dictates ATM activation via direct modification of its C terminus, whereas MOF regulates ATM activity through H4K16 acetylation. MOF interacts with ATM: MOF deletion results in defective ATM autophosphorylation and the ATM-dependent DNA damage response (Gupta et al. 2005). Mice with MOF-deficiency in Purkinje cells display a neurological disorder similar to A-T patients (Kumar et al. 2011), suggesting a functional synergy between MOF and ATM in the DNA damage response. *Zmpste24* null mice, with defective MOF function and hypoacetylation at H4K16, also exhibit an impaired response to DNA damage and cellular senescence: this phenotype can be rescued by MOF reintroduction and exposure to HDAC inhibitors (Krishnan et al. 2011). Nuclear c-Abl tyrosine kinase, which induces chromatin structural changes through H4K16 hypoacetylation, mediates ATM activation through phosphorylation of TIP60, thus coupling chromatin sensing to ATM signaling (Aoyama et al. 2011; Kaidi and Jackson 2013). The E3 ligases RNF8 and CHFR synergistically regulate ATM activation through histone ubiquitination and H4K16 acetylation (Wu et al. 2011). DNMT1-associated protein 1 (DMAP1), a member of the TIP60-p400 complex, is required for efficient ATM activation in response to DNA damage and hypotonic stress through regulation of H4K16 acetylation (Penicud and Behrens 2014). These reports strongly support that H4K16 acetylation is a pivotal factor involved in the onset and amplification of ATM signaling, mainly through its role in reshaping the local chromatin environment.

Other histone residues are also acetylated and implicated in the ATM-dependent DNA damage response. For example, TIP60-mediated H2AX acetylation at lysine 5 permits its ubiquitination, which further stimulates histone exchange and the DNA damage response (Ikura et al.

2007). In addition, H2AX acetylation is required for NBS1 turnover at DNA damage sites, which may restrict γH2AX expansion to undamaged regions (Ikura et al. 2015). These data suggest an indirect role for H2AX acetylation in fine-tuning ATM activation. In yeast, histone H4 acetylation at multiple sites, including lysines 5, 12 and 91, is also required for a proper DNA damage response, as mutating these lysine residues causes defective γH2AX domain formation and poor cell survival upon DNA damage (Ge et al. 2013). Histone H3 lysine 56 (H3K56) acetylation, which marks newly synthesized histones, is induced by DNA damage and shows a perfect co-localization with γH2AX (Das et al. 2009; Vempati et al. 2010), indicating a positive role for H3K56 acetylation in the DNA damage response. Later studies have demonstrated that H3K56 is specifically deacetylated at DNA damage sites by the instantly recruited histone deacetylases, HDAC1/2 and SIRT6 (Miller et al. 2010; Toiber et al. 2013), suggesting a dynamic nature of DNA damage-induced H3K56 acetylation. H3K9 acetylation similarly decreases upon DNA damage and constitutive H3K9 hyperacetylation impairs ATM activation in embryonic stem cells (Tjeertes et al. 2009; Meyer et al. 2016). p53-dependent H3K9 and H3K27 acetylation at sub-telomeric regions prevents γH2AX signal accumulation at telomeres (Tutton et al. 2016), suggesting a potential role for histone acetylation in restraining the ATM-dependent DNA damage response in specific chromosomal regions. Recently, we showed that acetylation of linker histone H1, a less-characterized chromatin mark, may also participate in regulating chromatin structure and genome stability in the DNA damage response (Li et al. 2018). Together, these studies show that histone acetylation is mainly implicated in ATM activation through altering local or general chromatin structure, and eventually controls a wide aspect of the DNA damage response and DNA repair.

Histone ADP-ribosylation

ADP-ribosylation is mediated by a group of poly-(ADP-ribose)-polymerases (PARPs), with PARP1 being the most prominent and best characterized. Unlike phosphorylation, methylation or acetylation, ADP-ribosylation is the transfer of one ADP-ribose moiety (mono-ADP-ribosylation) or polymeric ADP-ribose chains (poly-ADP-ribosylation, PARylation) to acceptor proteins (Hottiger 2015). Known acceptors in eukaryotic cells include lysine, arginine, glutamate, aspartate, cysteine, serine and asparagine residues, but the specificity remains ambiguous (Messner and Hottiger 2011; Rosenthal and Hottiger 2014). ADP-ribosylation is reversible via the action of ADP-ribose removing enzymes and tends to be more labile and transient than other small covalent modifications, which only last for a short time in vivo (Hottiger 2015; Koch-Nolte et al. 2008). The fact that only a small fraction (~4%) of histones is ADP-ribosylated adds up the complexity of dissecting the functions of site-directed histone ADP-ribosylation in DNA damage and repair (Boulikas 1989). Most previous studies have focused on the modifying enzymes PARP1 and PAR glycohydrolase (PARG). PARP1 is one of the earliest sensors of DNA breaks, being activated within seconds of detecting damage (Polo and Jackson 2011). PARP1 deletion or inhibition results in hypersensitivity to DNA damage inducers and compromised ATM activation (de Murcia et al. 1997; Bryant et al. 2005; Haince et al. 2007). PARP1-dependent chromatin decondensation is also one of the earliest events in the DNA damage response, which may license the spreading of phosphorylation signals, as chromatin compaction restricts the intensity of DNA damage signaling (Murga et al. 2007). PARG, the principal enzyme to hydrolyse PAR chains, is also recruited to DNA damage sites (Mortusewicz et al. 2011). PARG deletion or inhibition enhances γH2AX foci formation, p53 activation, and sensitizes cells to DNA damage (Shirai et al. 2013; Gravells et al. 2017, 2018), indicating a positive link between PARG and ATM activation.

The primary histone ADP-ribosylation targets upon DNA damage are histone H2A and H3, with a minor amount of other histones, such as H1 and H4 (Messner and Hottiger 2011; Jungmichel et al. 2013). Although information of site specificity is limited, recent studies using a series of proteomic screening methods have unraveled several sets of ADP-ribosylation targets under stressed conditions and revealed that serine is the major target on histones upon DNA damage (Leidecker et al. 2016; Palazzo et al. 2018; Fontana et al. 2017). Very recently, we identified that PARylation of linker histone H1.2 at serine 188 (S188) mediates H1.2 dynamics and is required for ATM activation upon DNA damage (Li et al. 2018) (Fig. 3). Mechanistically, H1.2 inhibits ATM activation and recruitment through a direct interaction and an MRN-dependent mechanism (Li et al. 2018). In response to DNA damage, H1.2 is PARylated, which allows its dissociation from chromatin and permits the interaction between ATM and MRN, thus facilitating robust ATM activation (Li et al. 2018). Therefore, we provided the first evidence of site-directed histone ADP-ribosylation in regulating ATM activity and the DNA damage response. While more information is still emerging, explorations of other histone ADP-ribosylation sites in DNA damage and crosstalk with other PTMs are of particular interest.

Histone ubiquitination

Similar to ADP-ribosylation, ubiquitination involves the covalent conjugation of a conserved 76-residue polypeptide (mono-ubiquitination) or polypeptide chains

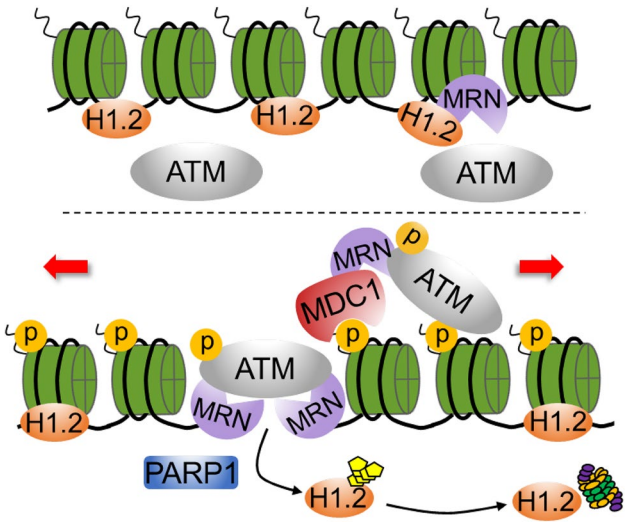

Fig. 3 Regulation of ATM activation by linker histone H1.2 PARylation and destabilization. In the absence of DNA damage, the chromatin-binding H1.2 prevents ATM recruitment and activation through the competing interaction with MRN complex. Upon DNA damage, H1.2 is PARylated by PARP1 and disassociated from chromatin for degradation, thereby permitting the recruitment and activation of ATM by MRN complex and DNA breaks. The activated ATM is amplified by an ATM-MDC1-MRN positive feedback loop, leading to efficient DNA damage response and repair

(poly-ubiquitination) to target proteins. Ubiquitination is sequentially catalyzed by a group of enzymes including: an E1 activating enzyme, an E2 conjugating enzyme and an E3 ligase that specifically transfers the ubiquitin to substrates, which may eventually alter protein function or stability (Zheng and Shabek 2017). As versatile as ubiquitination may be, histone ubiquitination is extensively involved in chromatin-based cellular processes, such as the DNA damage response and repair. As a crucial part of the hierarchical chromatin signaling network guiding the DNA damage response and repair, histone ubiquitination facilitates the enrichment of several key repair factors, such as 53BP1, onto damaged chromatin (Uckelmann and Sixma 2017). For example, H2A/H2AX ubiquitination at lysine 13/15 (K13/15) by RNF168 is required for repair factor loading, including 53BP1, which is a specific reader of the H2A K15 ubiquitination mark (Mailand et al. 2007; Huen et al. 2007; Kolas et al. 2007; Mattiroli et al. 2012; Wilson et al. 2016). Later studies have shown that RNF168 recruitment is dependent on RNF8-mediated ubiquitination of linker histone H1, which is recognized by RNF168 through its ubiquitin-dependent DSB recruitment module (UDM) (Thorslund et al. 2015). Nevertheless, a very recent study showed that lethal (Savitsky et al. 1995) malignant brain tumor-like protein 2 (L3MBTL2), rather than histone H1, is involved in the sequential RNF8 and RNF168 recruitment and ubiquitin signal amplification in response to DNA damage (Nowsheen et al. 2018).

Although generally believed to function downstream of phosphorylation, histone ubiquitination is also reported to impact on ATM full activation through certain de-ubiquitination feedback loops. For example, USP22 is a member of the de-ubiquitination module of the Spt-Ada-Gcn5-acetyltransferase (SAGA) complex, and is required for γH2AX foci formation through H2B de-ubiquitination at lysine 120 (K120) (Ramachandran et al. 2016). As H2B K120 ubiquitination is dependent on ATM-mediated phosphorylation of the RNF20/RNF40 heterodimer (Moyal et al. 2011), these studies suggest a possible feedback loop centered on H2B ubiquitination that regulates ATM activation. More recently, we, together with other researchers, found that accumulation of p62, an autophagic cargo protein, inhibits RNF168 activity and leads to impaired H2A ubiquitination, which eventually disrupts ATM activation and signaling upon DNA damage (Walker et al. 2017; Wang et al. 2016).

Other modifications

Various other types of histone modifications have also been implicated in the DNA damage response and DNA repair. For example, ubiquitin-like modifications (UBLylations), which conjugate ubiquitin-like proteins to target acceptors, including small ubiquitin-like modifiers (SUMOs) and neural precursor cell expressed, developmentally downregulated 8 (NEDD8), have been identified in histones in the context of DNA damage (Wang et al. 2017). NEDDylation of histone H4 and H2A differentially impacts RNF168-dependent H2A ubiquitination, which alters the DNA damage response and repair (Ma et al. 2013; Li et al. 2014). Although more details are needed, SUMOylation orchestrates the loading of histone-modifying enzymes onto chromatin during the DNA damage response (Hendriks et al. 2015; Huang et al. 2016), which might regulate ATM activation through crosstalk with other histone modifications. Specifically, the yeast H2A variant, H2A.Z-2 is SUMOylated upon DNA damage and facilitates its exchange at damage sites (Fukuto et al. 2018), with a possible involvement in reshaping the local chromatin state and thus promoting the DNA damage response.

Histone acylation is a less well-characterized histone mark that is extensively implicated in metabolic regulation (Sabari et al. 2017), but is also involved in the DNA damage response and repair. For example, sirtuin 7 (SIRT7), a class III HDAC, regulates chromatin compaction and the DNA damage response by desuccinylating core histones at DNA damage sites (Li et al. 2016). Histone succinylation alters chromatin structure and nucleosome dynamics in a similar manner to acetylation (Sabari et al. 2017; Jing et al. 2018), thus it may also guide ATM activation in a

similar way. Histone crotonylation, although not yet implicated in DNA damage, is also regulated and interpreted in an acetylation-resembled way and acts in combination with other histone modifications (Tan et al. 2011; Sabari et al. 2015; Zhao et al. 2016; Li et al. 2016; Andrews et al. 2016; (Xiong et al. 2016), which may be engaged in DNA damage response like acetylation. In addition, DNA damage-induced O-GlcNAcylation of H2A at serine 40 (S40) interacts with acetylated H2AZ and γH2AX at the initial phase of the DNA damage response, and is required for the accumulation of DNA damage response and repair factors (Hayakawa et al. 2017).

Conclusions and perspectives

Histones are subjected to numerous types of modification that regulate different aspects of cellular functions. The reversible and dynamic nature of histone modifications, with an upsurge in identifying novel modifications and their regulators, weaves a massive and multilayered molecular network to spatio-temporally regulate cellular responses in distinct contexts. In response to DNA damage, histone modifications protect genetic integrity and genomic stability through various mechanisms. Overall, we can conclude that ATM signaling is regulated by histone modifications to achieve three main aims (Table 1): (i) to create a chromatin mark (such as γH2AX and H3K9me3) to directly anchor or alienate ATM or its regulators; (ii) to reshape local chromatin structure (such as via most histone acylation marks) such that it indirectly affects ATM activation or recruitment; (iii) to alter ATM interactions (such as via H1 PARylation) with its regulators. While some histone modifications dictate ATM activation alone, it is noteworthy that most of them act and crosstalk with other modifications, which may elicit diverse effects than when operating alone. It is therefore more reasonable to consider histone modifications as combinations or clusters in the context of chromatin, rather than as a single epigenetic mark.

Our knowledge in histone modifications has grown exponentially over the past few years thanks to the development of high-throughput proteomic technologies. A major hinderance to delineate a clear and sequential effect of histone modifications in the DNA damage response is the lack of site-specific information, especially for non-canonical modifications, such as UBLylation and PARylation. Even if the modification site is known, it is usually challenging to create a site-directed mutation in mammals because mammalian cells express multiple copies of histone genes. In addition, mutagenesis assays can be pleiotropic and artificial, and thus may not represent the true function of the modification under analysis. Therefore, most studies have focused on the modifiers and specific readers of histone modifications. Chemical ligation or synthesis of modified histone is also informative for biochemical studies, but this strategy is largely limited to in vitro analysis (Holt and Muir 2015). Novel strategies or methodologies are now warranted to better illuminate the precise functions of site-specific histone modifications.

Although much is known about ATM, how ATM activation is triggered upon DNA damage, as well as upon many other stresses, remains elusive. One of the main obstacles is a lack of structural details of ATM and its regulating complexes. Recent studies have illustrated the structures of yeast Tel1 and human ATM at a relatively low resolution but these still provide some additional mechanistic insights into ATM activation (Wang et al. 2016; Baretic et al. 2017; Lau et al. 2016). A higher resolution of ATM structure, which will reveal its conformational changes upon stress or binding with its regulators, is now necessary for a more comprehensive understanding as to how ATM is activated. More importantly, DNA damage-induced activation of ATM relies on its binding to chromatin, which is dynamically regulated by histone modifications. Another critical issue that remains to be addressed is how ATM becomes disassembled and deactivated when DNA damage repair is

Table 1 Histone modifications related to ATM initial and robust activation

Histone modification	Function	References
γH2AX	MDC1 recruitment and amplification of ATM signaling	Stucki et al. (2005); (Lou et al. 2006)
H3K9me3	TIP60 activation and subsequent ATM acetylation and phosphorylation	Sun et al. (2009)
H3K36me2	NBS1 and Ku70 recruitment and ATM robust activation	Fnu et al. (2011), Cao et al. (2016)
H3K36me3	LEDGF and TIP60 recruitment and H4K16 acetylation	Li and Wang (2017)
H4K20me2	53BP1 recruitment and potential ATM retention	Pei et al. (2011)
H3K14ac	ATM interaction with chromatin	(Kim et al. 2009)
H4K16ac	Local or general chromatin structure	Wu et al. (2011), Penicud and Behrens (2014)
H1.2S188 PARylation	ATM recruitment by MRN complex and activation	Li et al. (2018)
H2AK15 ubiquitination	53BP1 recruitment and potential ATM retention	Mattiroli et al. (2012), Wilson et al. (2016)

completed. Previous articles showed that PP2A and PP5, two phosphatases, both regulated ATM activity in vivo. PP2A interacts with ATM in undamaged cells and irradiation induces PP2A dissociation from ATM, resulting in loss of its phosphatase activity (Goodarzi et al. 2004). Unlike PP2A, PP5 interacts with ATM in a DNA damage inducible manner and a catalytically active PP5 mutant inhibits ATM activation (Ali et al. 2004). Interestingly, Shreeram et al. found that another phosphatase wild-type p53-induced phosphatase (Wip1) overexpression was sufficient to downregulate the activation of ATM through dephosphorylating ATM Ser1981 as cells repaired damaged DNA (Shreeram et al. 2006). Moreover, recently our group reported that the histone deacetylase SIRT7-mediated deacetylation was essential for dephosphorylation and deactivation of ATM (Tang et al. 2019). We propose a novel model of ATM deactivation regulated by SIRT7-mediated deacetylation and subsequent by WIP1-mediated dephosphorylation. It is reasonable that the inactivation of ATM should follow a well-organized process and this process needs for more experimentation. Questions that remain include what is the consequence of persistent activation of ATM, what are the serial molecular events that trigger ATM removal and deactivation, does histone modification participate in this process, and are there any other modifications of ATM involved besides dephosphorylation and deacetylation. All these questions need to be answered with delicate studies.

As we have learnt more about the physiological roles of ATM, it has been proposed to be an apical regulator of the cellular response to stresses as much as it is a central kinase in DNA damage (Shiloh and Ziv 2013). Various stresses activate ATM, including oxidative stress, hypotonic stress, hypoxia, insulin, nitrosative stress (Bakkenist and Kastan 2003; Guo et al. 2010; Tripathi et al. 2013; Gibson et al. 2005; Yang and Kastan 2000), but how ATM is activated in these settings remains largely unknown. Insights into the regulatory mechanisms of ATM activation will greatly extend our perception of ATM as a broader sensor of stresses and not just a DNA damage regulator. Understanding how ATM is regulated in the above-mentioned physiological conditions will also help us to identify more promising drug targets and manipulate ATM activity in pathologies related to these stresses.

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Compliance with ethical standards

Conflict of interest The authors declare no competing financial interests.

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