Histone Methylation and the DNA Damage Response

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Abstract

Preserving genome function and stability are paramount for ensuring cellular homeostasis, an imbalance in which can promote diseases including cancer. In the presence of DNA lesions, cells activate pathways referred to as the DNA damage response (DDR). As nuclear DNA is bound by histone proteins and organized into chromatin in eukaryotes, DDR pathways have evolved to sense, signal and repair DNA damage within the chromatin environment. Histone proteins, which constitute the building blocks of chromatin, are highly modified by post-translational modifications (PTMs) that regulate chromatin structure and function. An essential histone PTM involved in the DDR is histone methylation, which is regulated by histone methyltransferase (HMT) and histone demethylase (HDM) enzymes that add and remove methyl groups on lysine and arginine residues within proteins respectively. Methylated histones can alter how proteins interact with chromatin, including their ability to be bound by reader proteins that recognize these PTMs. Here, we review histone methylation in the context of the DDR, focusing on DNA double-strand breaks (DSBs), a particularly toxic lesion that can trigger genome instability and cell death. We provide a comprehensive overview of histone methylation changes that occur in response to DNA damage and how the enzymes and reader proteins of these marks orchestrate the DDR. Finally, as many epigenetic pathways including histone methylation are altered in cancer, we discuss the potential involvement of these pathways in the etiology and treatment of this disease.

Keywords

Chromatin; DNA damage; DNA repair; Histone methylation; Genome stability

1. Introduction

The nuclear DNA of eukaryotic cells consists of duplexed DNA wrapped around histones and organized into chromatin [1]. In addition to compacting the genome into the limited volume of the nucleus, chromatin controls the accessibility to our genetic information,

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Conflict of interests

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resulting in the requisite involvement of chromatin in DNA-based processes including transcription, replication and DNA repair [2]. Our genomes must be faithfully duplicated and maintained, which can be challenging due to the hostile endogenous and exogenous DNA damaging agents that can be found in cells. Sources of DNA damage include replication errors, base damage, reactive metabolic products, as well as chemicals and radiation, which may include UV rays from sunlight or radiation that is commonly administered to cancer patients [3]. DNA damage not only threatens the maintenance and stability of our genome but can also affect our epigenome, which can collectively impair cellular and organismal homeostasis leading to various diseases including cancer [3]. To combat these ever-present dangers to our DNA, cells have evolved DNA damage response (DDR) pathways that detect, signal and repair DNA lesions [3, 4]. The importance of the DDR is highlighted by the fact that mutations in DDR pathways are commonly found in many different human diseases, such as cancer, neurodegenerative disorders and immune deficiencies [3, 5, 6].

Eukaryotic cells contain several different DNA repair pathways that engage and repair the wide-variety of DNA lesions that can occur across the genome. For example, UV-induced DNA lesions or other bulky lesions are repaired by nucleotide excision repair (NER) [7], while DNA mismatch repair (MMR) is used to correct base-base mismatches or insertion/ deletion loops generated during DNA replication [8]. The most genotoxic DNA lesion is the DNA double-strand break (DSB), which results in breakage of both DNA strands. In addition to promoting apoptosis and cell death, the dangers to DSBs are many and include degradation or aberrant religation of free DNA ends resulting in the loss of genetic information either through mutation or chromosome loss as well as chromosomal translocations. Eukaryotic cells use two primary pathways to repair DSBs: non-homologous end-joining (NHEJ) and homologous recombination (HR) [9], while several alternative pathways can also join DSBs [10]. NHEJ repairs DSBs throughout the cell cycle using a non-templated, religation repair mechanism that requires little to no processing of the DNA ends [11]. HR on the other hand engages a homologous DNA sequence as a template to repair the DSB in a more error-free manner. HR repair is mainly limited to the S and G2 phases of the cell cycle, a time when a homologous sister chromatid is readily available [12–15].

It is important to consider that DNA damage and the DDR occurs within the chromatin environment [16]. Specifically, approximately 146 bp of nuclear DNA is wrapped around the histone octamer containing two copies each of the core histones, H2A, H2B, H3 and H4, to form the nucleosome, which makes up the basic unit of chromatin [1, 17]. Chromatin structure and function is regulated by post-translational modifications (PTMs) of histones. Indeed, histones are covalently modified by a series of chemical and small protein modifications (e.g. phosphorylation, acetylation, methylation, ubiquitylation and SUMOylation) that are dynamically added or erased on particular histone residues by chromatin modifying enzymes to regulate chromatin-based processes (Fig. 1) [2, 18–20]. Histone PTMs can affect chromatin structure by altering interactions between nucleosome components including histones and DNA, as well as how histones interact with other histones. Histone PTMs also regulate interactions between chromatin proteins and nucleosomes by their ability to act as docking sites for chromatin "reader" proteins that

contain various PTM binding domains (Fig. 1) [2, 21, 22]. Altered histone modifications and mutations within chromatin binding factors are commonly observed in various diseases, which raises the important question of whether or not these mutations affect the DDR in addition to other chromatin-based processes [6, 23–28].

In addition to the well-established role of histone PTMs in transcription, histone marks including phosphorylation, acetylation, methylation, ubiquitylation and SUMOylation participate in key DDR functions [29–34]. Many histone PTMs are dynamically regulated by DNA damage. For example, one of the first histone modifications identified in the DDR was the phosphorylation of the histone variant H2AX. Upon DNA damage, this histone variant is phosphorylated on Ser139 (called γH2AX) [35] by the DDR related PIKK kinases (ATM, ATR and DNA-PK). This mark can be directly recognized by the BRCT domains of MDC1 to mediate downstream DDR signaling and recruitment of repair proteins [36]. 53BP1 is a key regulator of DSB repair pathway choice and a bivalent reader of histone modifications [37, 38]. While first shown to bind H3K79 methylation, 53BP1 recognizes DSB lesions through its interaction with H4K20me2 and H2AK15ub [39–41]. While these examples illustrate how histone PTMs provide interaction platforms for the accumulation of DDR factors surrounding damaged chromatin to orchestrate the DDR, histone PTMs can also modulate chromatin structure to facilitate repair [42]. The past decade has seen a flurry of studies establishing the role of chromatin and its modifications in promoting the DDR. However, additional mechanistic insights for understanding the relationship between chromatin and the DDR in the context of promoting genome and epigenome stability are warranted. These studies are particularly necessary to understand the interplay between the DDR and chromatin in human diseases including ageing and cancer [3, 6, 28, 34, 43].

First discovered in the 1960's, histone methylation is a common histone mark that occurs by the addition of a methyl group (–CH3) onto a lysine or arginine amino acid residue (Fig. 1) [44, 45]. Methylation can be added as mono- (me), di- (me2) or tri- (me3) on the ε-amino group of lysine; while arginine methylation can be mono-methylated (me) or di-methylated symmetrically (me2s) or asymmetrically (me2a). Histone methylations are catalyzed by histone methyltransferase (HMTs) enzymes, which are capable of adding a methyl group donated from S-adenosylmethionine to their target residue [45]. Currently, HMTs are classified into three families, which include the SET-domain containing enzymes and Dot1-like proteins that act on lysines (KMTs) [46]. The third family consists of arginine N-methyltransferase enzymes (PRMTs), which methylate arginines [47–49]. HMTs methylate histones incorporated into chromatin, but free histones and non-histone proteins can also be their substrates [50]. Histone demethylases (HDMs) are enzymes that remove the various methyl groups from lysines or arginines [51, 52]. Lysine demethylases (KDMs) are organized into two families: the amine oxidases and jumonji C (JmjC)-domain containing iron-dependent dioxygenases [53–55]. Arginine demethylases are less well characterized. JMJD6 has been proposed to be an arginine demethylase [56]; however its precise biological function remains unclear [57]. It has also been reported that a subset of JmjC KDMs can demethylate arginines [58]. The dynamic regulation of histone methylation has been reported to occur in transcription and other biological processes including the DDR [2, 22, 46, 49, 51, 52]. Aberrant histone methylation is also observed in human diseases (i.e. cancer) [45, 47, 59, 60]. Methylation is the only known modification that occurs on the three

molecules of the central dogma - DNA, RNA and proteins [61–65]. While DNA and RNA modifications have been implicated in the DDR [66, 67], in this review, we will focus on our current understanding of histone methylation and its involvement in the DDR. We will cover in-depth how KMTs and KDMs regulate histone methylation in response to DNA damage and how these changes promote the DDR in mammalian cells. Chromatin factors, including histone methylation pathways, and DDR proteins are areas of intense research for their potential as therapeutic targets for human diseases including cancer [6, 23, 25, 68–70]. Obtaining a mechanistic understanding of the interplay between histone methylation and DDR pathways can inform the development and use of DDR and chromatin targeting therapies in disease-relevant settings.

2. Histone methylation and the DDR

Histone methylations are most well studied for their roles in transcriptional regulation [71–73]. Currently, evidence has mounted that these histone marks also play important roles in the DDR. DNA damage-mediated methylation dynamics have been identified on several lysine residues including histone H3 Lysine 4 (H3K4), H3K9, H3K27, H3K36, H3K79 and histone H4 lysine 20 (H4K20me2) (Fig. 2). Numerous KMTs and KDMs have been observed to rapidly accumulate at DNA damage sites (Table 1). It also appears that pre-existing methylation marks may serve multiple functions in both DNA damage and transcriptional regulation (i.e. H3K36me3). Here we review our current understanding of these histone methylations and the enzymes that regulate them in the DDR.

2.1. H3K4 methylation

H3K4me3 is a histone mark associated with active transcription [73]. DNA damage has been shown to silence local transcription to facilitate DNA repair [74, 75]. These findings suggest that the chromatin environment that promotes transcription needs to be readjusted to a chromatin state that facilitates DNA damage signaling and repair in the presence of DNA lesions. In support of this idea, demethylation of H3K4me3 at DNA damage sites has been shown to be an important step for this damage-induced chromatin state transition [76–79]. Numerous KDMs that demethylate different H3K4 states are recruited to DNA damage sites where they have been reported to promote various DDR functions (Table 1) [76–79]. KDM5B (JARID1B) demethylates H3K4me2/3 and was found to accumulate at I-SceI-induced DSB sites in a PARP1 and macroH2A1.1 dependent manner [76]. Loss of KDM5B impairs DSB repair factors Ku70 and BRCA1 accumulation at DSBs resulting in defective NHEJ and HR repair. The enzymatic demethylation activity of KDM5B is required for efficient DSB repair, since a catalytically dead mutant of KDM5B cannot support NHEJ and HR repair. However, whether or not H3K4me2/3 is the critical or sole target of KDM5B in DSB repair remains to be determined [76]. A recent study reported the DDR functions of KDM5A (JARID1A or RBP2), another H3K4me2/3-specific KDM [78]. This study identified KDM5A-mediated demethylation on H3K4me3 as an important step for facilitating the recruitment of the ZMYND8-NuRD chromatin remodeling complex to DSB sites, a complex that has been shown to locally repress transcription around DSBs (Fig. 3A) [78, 80]. Consistent with phenotypes associated with the loss of ZMYND8-NuRD components, cells lacking KDM5A exhibit impaired transcriptional repression at DSBs and

HR repair [78]. In addition, KDM5C (JARID1C), another KDM in the KDM5 family, is also involved in the DDR [79]. In response to the alkylating agent methyl methanesulfonate (MMS), which results in replication stress [81], KDM5C is modified by SUMO-2 [79]. SUMOylation helps to recruit KDM5C to chromatin where it demethylates H3K4me2/3 to maintain chromatin in a repressed state upon MMS treatment. Interestingly, KDM5B is also SUMOylated upon MMS treatment, but it triggers an RNF4-mediated ubiquitylation and degradation of KDM5B [79]. Thus, although related, these KDMs appear to play different roles in the DDR depending on the type of DNA damage. In addition to its regulation at DSB sites, H3K4me3 changes might also impinge upon transcription responses that are associated with various types of DNA damage. The functional significance of H3K4me3 demethylation by this family of demethylases in response to DNA damaging agents warrants further investigation.

LSD1 (KDM1A), the first lysine demethylase identified, targets H3K4me1/2 [53]. LSD1 is known to function in the DDR as it accumulates at laser and restriction enzyme-induced DSB sites [77]. The DDR function of LSD1 is unique compared to H3K4me2/3 specific KDMs [76, 78, 79]. LSD1 physically interacts with the E3 ubiquitin ligase RNF168 and requires RNF168 for its damage recruitment and DDR function, including demethylation of H3K4me2 at damage sites specifically in S/G2 cells. LSD1 does not regulate ionizing radiation-induced foci (IRIF) formation of γH2AX, MDC1 or BRCA1; however, it has been shown to promote H2A/H2AX ubiquitylation and 53BP1 IRIF formation in late S/G2 cells. Additionally, unlike KDM5A and KDM5B that facilitate HR, loss of LSD1 leads to increased HR repair levels as observed using the cell-based DR-GFP assay, suggesting that LSD1 may limit HR repair [77]. Although these studies provide a framework for understanding H3K4 methylation in the DDR, it will be important to decipher how different states of H3K4 methylation are regulated and coordinated to make the chromatin landscape conducive to orchestrating various DNA repair pathways. In contrast to our understanding of KDMs in the DDR, very little is known about DDR functions of KMTs that modify methylations on H3K4. One study has reported that RNF20-mediated H2B ubiquitylation promotes the methylation of H3K4 at I-SceI-induced DSBs to support HR, although the specific KMT(s) involved in this regulation have not yet been identified [82]. In addition, MLL4, an H3K4-specific KMT, has been proposed to protect acute myeloid leukaemia (AML) cells from ROS and DNA damage induced differentiation, suggesting that MLL4 functions in pathways important for both genome stability and cancer [83].

2.2. H3K9 methylation

Trimethylated H3 lysine 9 (H3K9me3) is a mark associated with gene silencing and heterochromatin [73, 84]. Several H3K9-specific KMTs, including SUV39H1 (KMT1A), SETDB1 (KMT1E) and PRDM2 (KMT8A or RIZ1) have been found to accumulate and mediate the enrichment of H3K9me2/3 around DNA DSB sites, which provides strong evidence for the involvement of these KMTs in the DDR [85–88]. Enrichment of H3K9me3 at DNA damage sites has been proposed to serve several purposes. For example, TIP60, a histone acetyltransferase (HAT) that functions in DSB repair, can directly bind to H3K9me3 at damage sites through its chromodomain [85]. This interaction increases the HAT activity of TIP60, which acetylates ATM and H4 to support HR repair [85, 89]. H3K9me3 also

provides binding sites for a complex containing the histone methyltransferase SUV39H1, KAP1 and HP1 at DSBs [86]. Recruitment of this complex to damage sites facilitates the spreading of H3K9me3, which is catalyzed by SUV39H1, to transiently form H3K9me3 at DSBs, which further activates TIP60 and TIP60-mediated ATM signaling. Activated ATM then phosphorylates KAP1 to release the SUV39H1-KAP1-HP1 complex from damaged chromatin, which acts to control this complex through this negative feedback loop mechanism [86]. TIP60 also promotes HR repair by modifying histones. H4 and H2A acetylations by TIP60 occur around DSBs, which can compete with the binding of the DDR protein 53BP1 to damaged chromatin [89, 90]. Binding of 53BP1 to chromatin inhibits DNA end-resection thereby favoring NHEJ repair. The ability of TIP60 to acetylate histones to block 53BP1 binding is in agreement with its role in promoting HR. Furthermore, since H3K9me3 activates TIP60, cells depleted of SUV39H1 display decreased H4ac levels around DSB sites and impaired HR repair [86].

Methylation on H3K9 also collaborates with chromatin proteins, including the histone H2A variant macroH2A1, to form repressive chromatin around DSBs [88]. Following an RNAi screen to identify novel chromatin modifiers that regulate HR, Khurana et al found that macroH2A1 and KMT PRDM2 accumulated at DNA lesions, along with an enrichment of the PRDM2-mediated PTM H3K9me2 [88]. MacroH2A1 was shown to promote the recruitment of PRDM2 to DNA damage, suggesting that these factors function in the same pathway. Consistent with this idea, cells lacking either macroH2A1 or PRDM2 exhibited reduced recruitment of the HR factor BRCA1 to laser-induced DNA damage and impaired DNA end-resection, which further highlights the involvement of this repressive mark and these factors in mediating HR repair [88]. Whether this mark functions solely in modulating chromatin structure at damage sites and/or is read by a DDR factor to promote repair remains to be determined. The H3K9me2/3 KMT SETDB1 is also recruited to laser damage sites [87]. Similar to what is observed in SUV39H1 and PRDM2 deficient cells, loss of SETDB1 leads to diminished damage-accumulation of HR factors RPA and RAD51, which results in HR defects [87]. In contrast, two other H3K9me1/2 KMTs, G9a (KMT1C) and GLP (KMT1D) are degraded by the proteasome in response to DSBs induced by the TOPII inhibitor doxorubicin or in Ras-induced senescent cells. It is tempting to speculate that under these conditions, these KMTs may function either in the DDR or in transcriptional responses that require regulation of H3K9me2 to promote the biological responses to these stress conditions [91].

In addition to the involvement of several H3K9 methyltransferases in the DDR, KDM4B (JMJD2B) and KDM4D (JMJD2D), are recruited to damage sites, suggesting that the removal of methyl groups from H3K9 plays a role in the DDR [92, 93]. The damage recruitment of both of these KDMs relies on PARP1, a poly ADP-ribose polymerase that participates in diverse biological pathways including the DDR [92, 93]. Overexpression of KDM4B leads to a global loss of H3K9me3, but specific loss of H3K9me2 at damage sites, which has been proposed to enhance DSB repair efficiency and cell survival following γ-irradiation [92]. Although this study focused on overexpression of KDM4B, analysis of loss of function for KDM4B in the DDR has not been reported [92]. KDM4D was found to be directly PARylated by PARP1 in response to DNA damage induced by either etoposide or camptothecin.[93]. PARylated KDM4D may facilitate its association and/or activities at

DNA damage sites although additional studies are required to answer this question. For example, is KDM4D modified by PARP prior to its association with damage sites or post-damage accumulation? Regardless, loss of KDM4D in cells also impairs the chromatin association of ATM in response to DNA damage, which leads to defects in ATM-dependent signaling, including the phosphorylation of H2AX, KAP1 and CHK2. These cells also exhibit impaired RAD51 and 53BP1 IRIF formation and diminished HR and NHEJ, providing strong evidence for a central role of KDM4D in DSB repair [93]. Demethylation of KDM4D substrates appear to be important for HR, as a catalytically dead mutant of KDM4D exhibited similar HR deficiencies as cells lacking wt KDM4D [93]. In summary, although several reports have firmly placed H3K9 methylation as an important histone mark in the DDR, how damage-induced recruitment of KDM4B/KDM4D and demethylation of their substrate H3K9me2, coordinates with the damage recruitment of H3K9me2/3 KMTs is still unclear. The addition and removal of the same modification on a particular residue by DNA damage has also been documented for acetylation signaling involving H4K16 (i.e. HDAC1/2-mediated H4K16 deacetylation promotes NHEJ; while TIP60-mediated H4K16ac is important for HR repair) [89, 94]. How the methylation state on H3K9 facilitates DSB repair in the chromatin environment, including perhaps in DNA DSB repair pathway choice, is an interesting question to pursue in future investigations.

2.3. H3K27 methylation

H3K27me3 is associated with repressive chromatin and has been observed to accumulate within 5 min at damage sites generated by laser, as well as at restriction enzyme induced DSBs and H_2O_2-induced damage foci [95–97]. The lysine methyltransferase EZH2 (KMT6), a H3K27me2/3 specific KMT found in the PRC2 complex, is also recruited to damage sites where it catalyzes this histone methylation mark [95–98], although we cannot exclude the possibility that other H3K27 KMTs, like EZH1 (KMT6B), may also contribute to the damage-specific H3K27me3 enrichment. H3K27me3 may participate in promoting DNA damage associated transcriptional silencing, although this is yet to be tested. Upon I-SceI-induced DSBs or oxidative damage induced by H_2O_2, EZH2 accumulates at promoters of actively transcribed genes together with other silencing factors, including SIRT1, DNMT1 and DNMT3B [96, 97], which suggests it may function in repressing specific genes in response to DNA damage. The DNA damage recruitment of EZH2 is PARP-dependent [95, 98]. Interestingly, PARP plays an important role in damage-induced transcriptional repression, including by promoting the recruitment of the ZMYND8-NuRD chromatin remodeling complex to damage chromatin where it participates in repressing transcription in the vicinity of DSBs [80, 95, 99, 100], Given these results for other repressive complexes, we cannot rule out that PARP-mediated EZH2 recruitment and formation of H3K27me3 at damage sites may function in conjunction with other repressors to silence transcription and thereby facilitate DNA repair. It is likely that EZH2-mediated H3K27me3 may function as an important mechanism to coordinate transcription both at damage sites and in genes. These functions may be needed to simultaneously accommodate both transcription and DNA damage activities, possibly to facilitate repair of DNA lesions while also orchestrating transcriptional responses to DNA damage.

2.4. H3K36 methylation

Methylation on H3K36 has been show to be an important chromatin component of the DDR. While numerous KMTs can mono- and di-methylate H3K36, SETD2 (KMT3A) is the only known KMT responsible for the tri-methylation on H3K36 [101]. Genome-wide studies have identified H3K36me3 as a mark highly enriched on the gene bodies of actively transcribed genes, which is in line with its involvement in transcriptional elongation [73, 101, 102]. H3K36me3 has been linked to DNA repair occurring in transcriptionally active regions [103, 104]. Using a restriction enzyme to create site-specific DSBs, Aymard et al. found that DSBs in proximity to actively transcribed genes are preferentially repaired by HR and that H3K36me3 is involved in this repair process [103]. In response to DSBs, depletion of SETD2 and therefore H3K36me3 leads to decreased ATM and p53 phosphorylation, defective DNA end-resection, impaired damage recruitment of RPA and RAD51, and low HR efficiency [103–105]. Mechanistically, H3K36me3 has been shown to provide binding sites for the PWWP methyl reader domain of LEDGF (p75), a factor that promotes HR repair through its interaction with CtIP (Fig. 3B) [106]. Specifically, loss of SETD2 results in decreased chromatin bound LEDGF in response to DNA damage, which impairs CtIP recruitment resulting in defective end-resection and a concomitant reduction in the ssDNA binding proteins RPA and RAD51 at damage sites [103, 104, 106]. In support of H3K36me3 functioning in HR, overexpression of the H3K36me3 demethylase KDM4A (JMJD2A or JHDM3A) reduces HR efficiency in cells [104]. In contrast to H3K36me3, dimethylation on H3K36 is induced upon ionizing radiation (IR) and also accumulates around I-SceI generated DSBs, leading to increased accumulation of NHEJ factors to these lesions [107]. This study also identified Metnase (SETMAR), which contains a SET histone methylase domain, as a DNA damage factor that is recruited to I-SceI DSBs where it modifies H3K36me2 within the surrounding chromatin [107, 108]. Consistent with these findings, depletion of Metnase or overexpression of the H3K36me2-specific demethylase KDM2A (JHDM1A) impairs repair of DSBs by the NHEJ pathway [107]. Taken together, these results have revealed that di- and tri- methylation on H3K36 can strongly impact how DSBs are repaired, which highlights the intricate signaling mechanisms that govern chromatin-based DDR pathways that are orchestrated by histone methylation.

In addition to H3K36me2/3 KMTs being involved in the DDR, several studies have also described the functions of H3K36 KDMs, including KDM2A and KDM4A, in promoting DNA damage signaling and repair. DNA damage has been shown to induce the degradation of KDM2A and KDM4A, [109, 110]. KDM2A interacts with and is phosphorylated by ATM at threonine 632 upon DSB formation. Induction of this phosphorylation blocks the ability of KDM2A to bind to chromatin thereby inhibiting its histone modifying capabilities. The activation of this pathway increases H3K36me2 levels around DSB sites, which has been shown to facilitate the recruitment of the MRN (MRE11-RAD50-NBS1) complex to promote DNA repair [109]. DSBs also trigger RNF8- and RNF168-mediated degradation of the demethylase KDM4A [110]. Although degradation of KDM4A may regulate the DDR by inhibiting its activity towards H3K36 methylation [104], the loss of this enzyme may also serve another function in the DDR. KDM4A contains a tandem tudor domain which can read di-methylated H4K20, an important docking site for the DNA damage factor 53BP1 [111]. Thus degradation of KDM4A would reduce its binding to this mark, allowing for the

exposure of H4K20me2 to facilitate the recruitment of 53BP1 to DSBs [110]. Collectively, these data suggest the presence of DDR pathways that modulate both KMTs and KDMs H3K36 methylation activities. Although the potential combination of histone modifications is almost limitless, it appears that key histone residues play important roles in regulating interactions between factors involved in chromatin-based signaling, including those involved in the DDR. This appears to be a mechanism that allows for one template (i.e. chromatin) to regulate diverse DDR processes including DNA damage signaling and repair across the structural and functionally variable genome.

Besides its involvement in DSB repair as discussed above, SETD2-mediated H3K36me3 has also been shown to play essential roles in DNA mismatch repair (MMR), a repair system used to correct base-base mismatches or insertion/deletion loops generated during DNA replication [8]. Two major complexes, MutSα (MSH2-MSH6) and MutSβ (MSH2–MSH3) recognize mismatched base errors to initiate MMR in eukaryotic cells. In human cells, trimethylated H3K36 is critical for MMR initiation, since the PWWP domain of human MSH6 directly recognizes H3K36me3 to assist in the recruitment of the MutSα region (Fig. 3B) [112]. Cancer cells with mutated or depleted SETD2 fail to recruit MutSα to DNA lesions and display microsatellite instability, a phenotype associated with a defective MMR pathway [112]. Overexpression of three KDMs of the KDM4 family (KDM4A-C), which disrupt the balance of H3K36me2/3 in cells, results in impaired MSH6 foci formation during S-phase and leads to MMR defects, evident by microsatellite instability [113]. Thus, H3K36 methylation represents a key histone methylation mark that is utilized by several DNA repair pathways to ensure genome stability.

2.5. H3K79 methylation

Although most histone methylations occur on the tails of histones, H3K79 methylation is located in the core of the histone. Core histone modifications have been proposed to regulate chromatin structure and function, as well as potentially affect how histones interact with their chaperones [114]. In eukaryotic cells, mammalian DOT1L (KMT4) (or yeast Dot1) methylates H3K79, a pathway that has been found to be involved in numerous cellular functions, including transcription, DSB repair and cell cycle regulation [115, 116]. In budding yeast, Dot1-mediated H3K79 methylation has been shown to promote nucleotide excision repair (NER) in response to UV-induced DNA lesions [117]. Yeast Dot1 also performs multiple functions in the DSB repair, such as G1/S checkpoint activation upon IR and promoting the damage recruitment of Rad9, the yeast ortholog of 53BP1 [118]. These results indicate that H3K79 methylation plays a key role in yeast DNA damage signaling [41, 116]. In mammalian cells, although DOT1L-mediated H3K79me2 was reported to be important for 53BP1 binding in response to DSBs [41, 119], later studies have showed that the tandem tudor domain of 53BP1 preferentially binds to H4K20me2 at DSBs [37–39]. Thus, the precise function of DOT1L and H3K79 methylation in the DDR in mammalian cells awaits additional investigation.

2.6. H4K20 methylation

Unlike multiple lysine residues within H3 that are methylated, lysine methylation on H4 is restricted to lysine 20 [120]. The functional relevance of mono- and di-methylation of

H4K20 (H4K20me1/2) in the DDR are well established as they provide docking sites for the DDR factor 53BP1 [39]. However, H4K20me2 is one of the most abundant histone marks in mammalian cells, and whether or not this mark is increased at DNA damage sites or pre-existing methylation marks are involved in damage-induced 53BP1 binding has been a matter of debate. A further refinement of these models was necessary given the finding that the E3 Ub ligase RNF168 ubiquitylated H2A/H2AX on K15, which provides another binding site for 53BP1 [40, 121]. These results explained the observation that loss of RNF168 impaired 53BP1 binding to damage sites [122, 123]. Thus, bivalent recognition of both H2A/H2AXK15ub and H4K20me2 is required for the damage-specific recruitment of 53BP1 (Fig. 3C). Numerous other studies have identified KDMs targeting methylations on H4K20, including PR-SET7 (KMT5A or SETD8) and MMSET (KMT3G, WHSC1 or NSD2), which both accumulate at DSBs to regulate the local enrichment of mono- and di-methylation on H4K20 respectively [124–126]. Other studies have reported that MMSET efficiently methylates H3K36, but not H4K20 within a nucleosomal substrate [127]. Mouse embryonic fibroblasts (MEFs) lacking functional MMSET also show normal 53BP1 foci formation [128], suggesting a complex regulation of MMSET in regulating 53BP1 interaction at DSBs.

Several additional proteins, including the Polycomb protein L3MBTL1 and histone demethylase KDM4A, have been shown to compete with 53BP1 for H4K20me2 binding [129, 130]. DSBs appear to stimulate the eviction of L3MBTL1 by the chaperone VCP (p97) [131] and the removal of KDM4A by RNF8- and RNF168-mediated proteasomal degradation [110] to expose H4K20me2 and facilitate 53BP1 recruitment. Other mechanisms have also been proposed to regulate the binding of H4K20me2 by 53BP1 at DNA lesions. For example, acetylation on H4K16 prevents the interaction between 53BP1 and H4K20me2 to promote HR [89, 132]. In addition, two other H4K20me2/3-specific KMTs (KMT5B/C or Suv4-20h1/2) have also been shown to be involved in the DDR, since MEFs lacking these enzymes exhibit high H4K20me1 levels genome-wide, resulting in reduced 53BP1 foci upon IR and inefficient DSB repair [133]. Suv4-20h double-null B cells also show defects in immunoglobulin class-switch recombination (CSR), a process requiring an intact DSB repair system [133]. Taken together, these findings highlight the importance of H4K20 methylation in the DDR. Given that this methylated histone site is governed by several different enzymes, this raises the question as to where these reactions occur across the epigenome and whether or not these mechanisms are differentially utilized, either during the cell cycle or in different cells.

2.7. H2AXK134 methylation

Methylation marks on histone H2A and H2B are poorly characterized. However, it has been reported that dimethylation on H2AX lysine134 (H2AXK134me2) is involved in the DDR [134]. SUV39H2 (KMT1B) is a KMT that is highly expressed in many cancer cell lines [134]. Following an investigation on SUV39H2 gene expression in chemo- and radiosensitivity of several cell lines, Sone et al reported that SUV39H2 could di-methylate H2AXK134 both *in vitro* and *in vivo*. This methylation was proposed to be important for the survival of various cancer cell lines upon radio- or chemotherapeutic agents, since expression of the dominant-negative from of H2AX-K134A in Hela cells led to hyper-

sensitivity to ionizing radiation, cisplatin or doxorubicin treatments [134]. Mechanistically, H2AXK134me2 is critical for the formation of γH2AX in response to DNA damage. SUV39H2-null (SUV39H2$^{-/-}$) MEFs and cancer cells with SUV39H2 depletion displayed defective γH2AX and 53BP1 foci formation upon doxorubicin treatment [134]. However, the details for how SUV39H2 modifies H2AXK134 are still unclear [135]. For example, another study reported an inability to detect methylation on recombinant H2AX or peptides by SUV39H2 or its homolog SUV39H1 (KMT1A) *in vitro* [135], suggesting that additional factors may contribute to the regulation of this pathway.

2.8. Histone arginine methylation

Unlike the well-established role of histone lysine methylation in the DDR as discussed here, PRMT-mediated histone arginine methylation is currently poorly characterized in the DDR. It is surprising to note that there is only one report of DDR related arginine methylation, which involves PRMT7-mediated H2AR3me2 and H4R3me2 [136]. Together with the BRG1-containing SWI/SNF complex, PRMT7 is directly recruited to promoter regions of several DNA repair genes where it catalyzes the dimethylation on H2AR3 and H4R3 to negatively regulate the transcription of these genes. Cells lacking PRMT7 exhibit increased expression of DNA repair genes and enhanced resistance to DNA-damaging agents; while reducing expression of one of these repair genes, the catalytic subunit of DNA polymerase, POLD1, re-sensitized PRDM7-depleted cells to DNA-damaging agents [136]. Given that there are at least 9 arginine methyltransferases and several mechanisms have been proposed for methylation of arginines in mammalian cells [48], additional studies are needed to characterize the potential involvement of these pathways in the DDR.

3. Non-histone protein methylation and DNA damage pathways

Although we have focused on histone methylation, lysine methylations on non-histone proteins also function in various cellular functions, including the DDR [65, 137]. p53 is a critical DDR regulator that controls checkpoint activation, cell cycle arrest and apoptosis in response to DNA damage [138, 139]. p53 methylation is well-studied and provides a primary example of a functional lysine methylation on a non-histone protein that is involved in the DDR [140]. For example, DNA damage increases dimethylation of p53 on K382, which is recognized by the 53BP1 tandem tudor domains. This interaction stabilizes p53 upon DNA damages to facilitate its DDR functions [141]. These activities by 53BP1 involve p53-dependent responses and are unique from its DSB repair functions [142]. Recent studies have also reported that KDM-mediated demethylation of non-histone DDR factors are critical events involved in the DDR. Human demethylase JMJD1C (KDM3C) is recruited to DNA damage sites where it demethylates MDC1 on lysine 45, which promotes essential DDR signaling events including MDC1 and RNF168 interactions, RNF8-dependent ubiquitylation and recruitment of RAP80-BRCA1 to damage sites [143].

Arginine methylations on non-histone proteins have been implicated in different DDR pathways [144]. The protein arginine methyltransferase PRMT1 is an established facilitator of the DDR as several substrates of PRMT1, including MRE11, BRCA1 and 53BP1, play essential functions in DSB repair [145–147]. PRMT1 and PRMT6 also methylate arginine

residues on DNA polymerase β (Polβ), which promotes efficient base excision repair [148, 149]. Finally, a recent study identified DDR functions for PRMT5, which was shown to methylate RUVBL1, a coactivator of the TIP60 HAT. Arginine methylation of RUVBL1 by PRMT5 was shown to support the HAT activity of TIP60 towards H4K16 to facilitate HR repair, while loss of PRMT5 resulted in error-prone NHEJ and genome instability [150]. Thus, non-histone methylation of both lysine and arginine residues play important roles in orchestrating methylation signaling involved in the DDR.

4. Involvement of histone methylations in cancer epigenetics

Considering the critical functions of histone methylation in regulating transcription and the DDR, changes in methylation signaling resulting from misregulation of HMTs (KMTs and PRMTs) or KDMs could alter both gene expression and the DDR, two pathways known to be dysfunctional in cancer. Indeed, alterations in histone methylation and methylation signaling pathways are observed in cancer and are thought to be involved in this disease [59, 60, 68]. Consistent with this notion, over half of all human methyltransferases and demethylases have been associated with cancer and other diseases, which highlights the importance of this pathway in human health [60, 69]. A paradigm for this concept are HMT driven cancers involving the chromosomal translocation of members in the KMT2 family (or mixed lineage leukaemia [MLL]), which include translocation-generated MLL1 (KMT2A)-fusion proteins that contribute to approximately 10% of human leukaemias [151, 152]. MLLs (MLL1-6) catalyze methylations on H3K4 [45]. MLL-fusion proteins lose their KMT activities, but still retain MLL-associated DNA binding abilities and interaction partners, which can function as oncogenes to induce leukaemogenesis and mediate the self-renewal of malignant cells [152]. A recent study reported that MLL4 (KMT2D) is an essential driver in promoting self-renewal and protecting MLL-AF9 fusion-induced leukaemia from oxidative stress or DNA damage-induced differentiation of acute myeloid leukaemia (AML), a mechanism that can constrain malignant haematopoiesis and limit AML transformation [83]. In addition, MLL3/MLL4 were found to promote MRE11 nuclease mediated DNA degradation of stalled replication forks together with their interacting factor PTIP [153]. Loss of PTIP or MLL3/4 protects degradation of replication forks in response to replication stress, a mechanism thought to promote survival from genome instability that occurs in BRCA-deficient cells [153]. These studies also inform the use of chemotherapeutics to target these tumors as loss of these factors or fork protection reduces chromosomal aberrations associated with these treatments and fork protection is indicative of patient outcomes to platinum and PARP inhibitor treatments [153].

The H3K36me3-specific KMT SETD2 plays important functions in the DDR, but is commonly mutated across a range of human cancers [154]. For example, SETD2 is highly mutated in clear cell renal cell carcinoma (ccRCC), and has been identified as a tumor suppressor. Loss-of-function of SETD2 has been linked to tumorigenesis in this cancer [155–157]. Certain SETD2 deficient ccRCC cells have been shown to have MMR deficiency, even though no detectable mutations were identified in MMR genes, which is in agreement with SETD2-mediated H3K36me3 as a vital component of MMR [112]. Loss of SETD2 in ccRCC was found to correlate with aberrant replication and impaired DNA repair, further supporting the idea that SETD2 acts to maintain genome integrity and suppresses

cancer [158]. In addition to mutations in SETD2 that alter H3K36me3 levels, mutations in histone H3 that result in the formation of H3K36M, as well as H3K27M, have been identified in several cancers [159–161]. Although these mutations in H3, called "oncohistones", have only recently been identified, studies are starting to reveal how these mutant histones alter normal methylation patterns of histones to promote oncogenic processes in these tumor types [162–165]. Given the involvement of H3K36me3 in the DDR, it will be of interest to determine if oncohistones affect the DDR and if so, whether or not this could be used as a therapeutic strategy in these cancers. In addition, H3K36me3-deficient cancer cells and tumors caused by loss of SETD2 were shown to be synthetically lethal to an inhibitor (AZD1775) targeting the cell cycle factor Wee1 [166]. Inhibition of Wee1 using this drug can induce replication stress, abnormal mitosis and loss of genome integrity [167, 168]. This may provide a therapeutic advantage to cells with defective DNA repair pathways including in SETD2-deficient cells, findings that are being explored with Wee1 inhibitors in clinical trials [169].

Altered expression of KDMs, especially those targeting H3K4 and H3K27, are commonly observed in human cancers [59, 69]. Somatic mutations within KDM genes are not commonly found except in the KDM6A (UTX) gene [170]; while aberrant expression of KDMs is frequently observed in primary tumors. These facts have driven the development of understanding the catalytic mechanism of these enzymes for consideration as drug targets [69]. For example, the H3K4 specific KDM5 family has been shown to be mis-regulated in many cancers and also plays critical DDR functions as discussed earlier. Additionally, KDM5A is involved in promoting drug-tolerance of non-small-cell lung cancer (NSCLC) cells, including to DNA damaging agents used as chemotherapeutics [171] and KDM5B is commonly overexpressed in breast, prostate, and bladder cancers [52, 172]. Inhibition of KDM5 demethylases by small molecules can efficiently impair the survival of cancer cells [173–175]. Small molecule inhibitors of KDM5A also interfere with damage functions of the ZMYND8-NuRD complex, which together with KDM5A promote HR repair [78]. Similarly, KDM5B and KDM5C have also been shown to function in the DDR [76, 81]. It is unclear how changes in the expression of these demethylases affect the DDR in these cancer settings and how this contributes to the etiology and treatment of cancers. For example, it is reported that overexpression of KDM5B in breast cancer cells represses tumor suppressor genes, including BRCA1, to promote cancer cell proliferation. It is not known whether or not this scenario resulting in downregulated BRCA1 leads to HR deficiency in these cells [172]. Both ZMYND8 and components of the NuRD complex are commonly mutated or aberrantly regulated in cancers [176, 177]. Besides, ZMYND8 also interacts with KDM5C and KDM5D to modulate enhancer activity in breast cancers [178] and repress metastasis-promoting genes in prostate cancer [179]. It will be important to examine whether the DDR functions of ZMYND8, NuRD and KDM5s are defective in these cancers, which is an important consideration when studying epigenetic mechanisms that are involved in both the DDR and cancer [34].

5. Conclusions and perspectives

As summarized here, accumulating evidence has revealed the importance of histone methylation pathways in signaling and repairing DNA damage. Many histone

methyltransferases and demethylases are recruited to DNA damage sites where they act to modify chromatin to orchestrate chromatin-based DDR activities. For example, these activities control the recruitment of methylation reader proteins, including 53BP1, which recognize damage-specific modified histones allowing for their accumulation on chromatin within damage sites to facilitate lesion recognition and repair. However, additional work to further elucidate mechanisms of methylation signaling involved in the DDR is needed. For example, several methylation-modifying enzymes are shown to localize to DNA damage sites and act on the same substrate. This raises the question as to how these KMTs and KDMs are coordinated within chromatin to regulate the DDR. It is possible that these proteins act redundantly or perhaps uniquely depending on the chromatin state and genome location of the DNA damage in a context specific manner. It has also been shown that the same histone residue can regulate different DNA repair pathways dependent on the methylation state of this mark. This is exemplified by the finding that H3K36me3 is important for HR repair, while H3K36me2 is involved in NHEJ [103, 104, 107]. It is possible that distinct methylation readers recognize the different methylation marks on the same residue to promote DNA repair, although the mechanisms that govern this regulation of DSB repair by this histone mark need further investigation. It is also unclear how the recruitment of KMTs and KDMs to DNA damage sites is regulated. One upstream factor reported is PARP signaling, which is required for the damage recruitment of many KMTs an KDMs, including SUV39H1, EZH2, KDM5A, KDM5B, KDM4B, KDM4D [76, 78, 86, 92, 93, 95, 98]. However, the mechanistic details for how PARP activation triggers the recruitment of these enzymes to damage sites is unknown. Understanding the inter-relationship between PARP signaling and histone methylation would provide important insights into how these pathways are regulated to promote the DDR.

Recently, genomic and gene expression studies from sequencing of cancer genomes have implicated mutations or altered expressions/activities of epigenetic modifiers as critical events in cancer development [23, 59, 68]. The list of methylation regulators, including HMTs, HDMs and methyl-readers, involved in multiple types of cancer is mounting. For histone methylation, the identification of oncohistones, include H3K27M and H3K36M, in various cancers has dramatically altered our perception for how alterations in histone methylation can be involved in cancer [180]. Finally, targeting methylation pathways has emerged as a promising strategy for cancer therapy, especially given that multiple KDM inhibitors have been created and are progressing from pre-clinical studies into clinical trials [69]. In addition to targeting epigenetic mediators, targeting DDR factors is also a promising field for drug development. This has been demonstrated by the recent FDA approval of PARP inhibitors for the treatment of HR deficient ovarian cancers [181]. Giving the success of PARP inhibitors in treating HR-deficient cancers and the emerging connections between PARP, histone methylation, the DDR and cancer, obtaining a better understanding of these pathways is needed. Thus, elucidating the molecular mechanisms of DNA repair pathways involving methylation signaling could reveal new and selective therapeutic approaches to target cancers; which may include those that display DDR and methylation defects.

Acknowledgments

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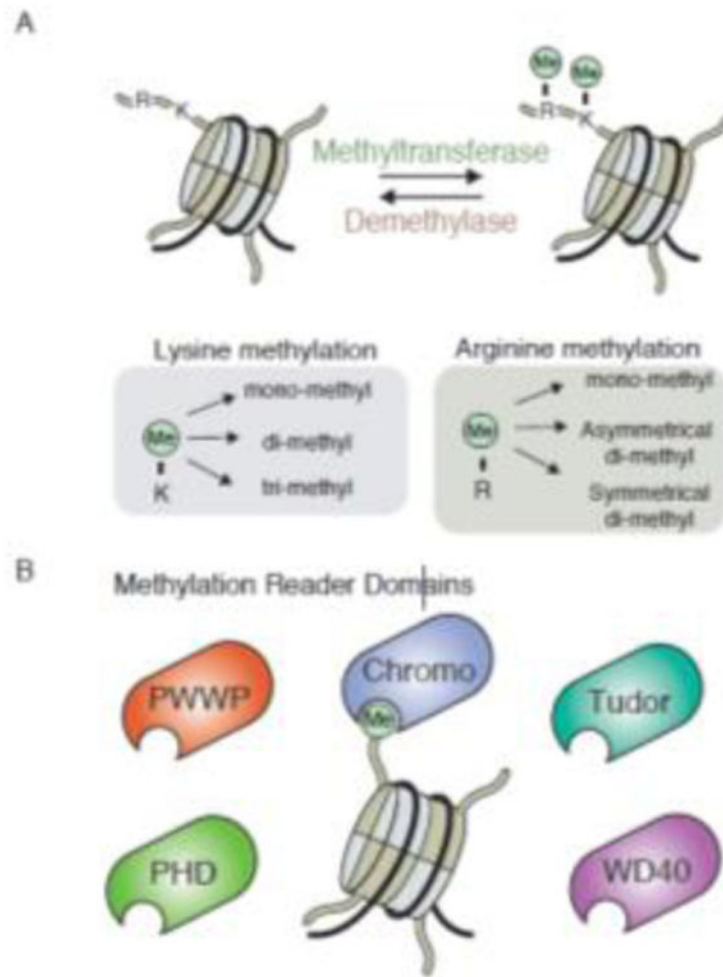
Fig. 1.
Histone methylation. (A) Histone methyltransferases (HMTs) catalyze the addition of methyl (−CH3) groups to histone lysines or arginines and histone demethylases (HDMs) reverse this reaction. Lysine or arginine methylation states are indicated. (B) Methylated histones can be recognized by proteins containing various methyl-binding reader domains, such as PWWP, chromodomain, PHD, Tudor and WD40, which are summarized in [22].
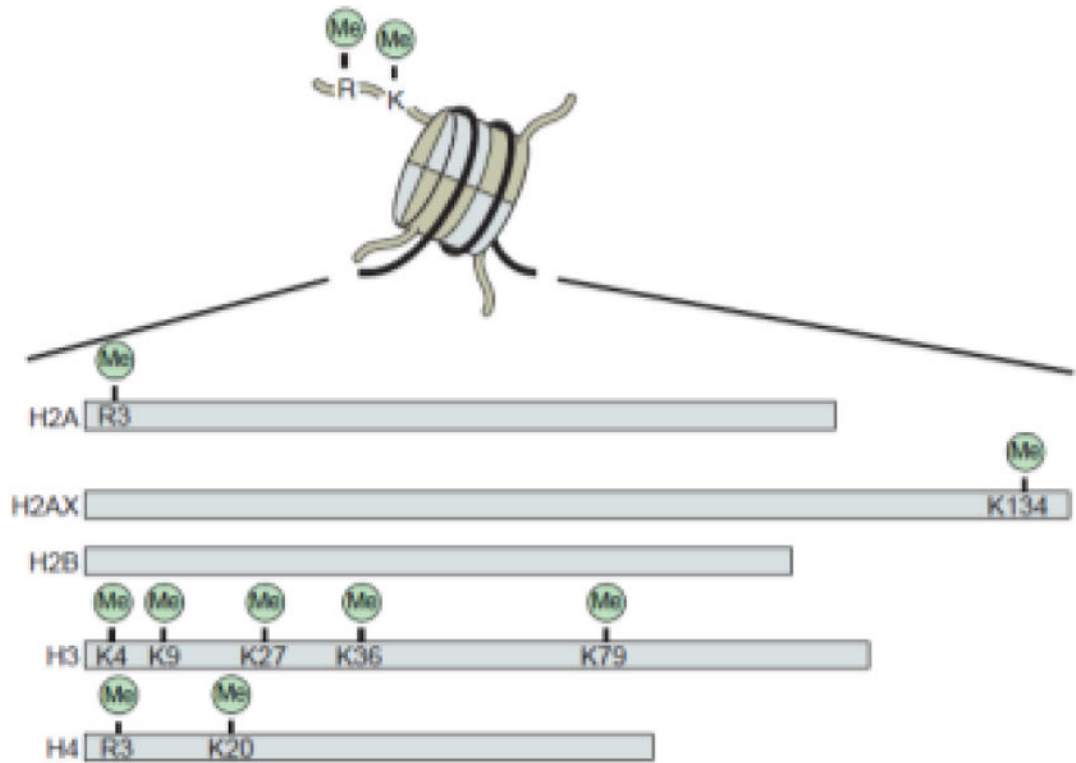
Fig. 2.
DNA damage associated histone methylations. Histone methylation sites involved in the DDR are shown.
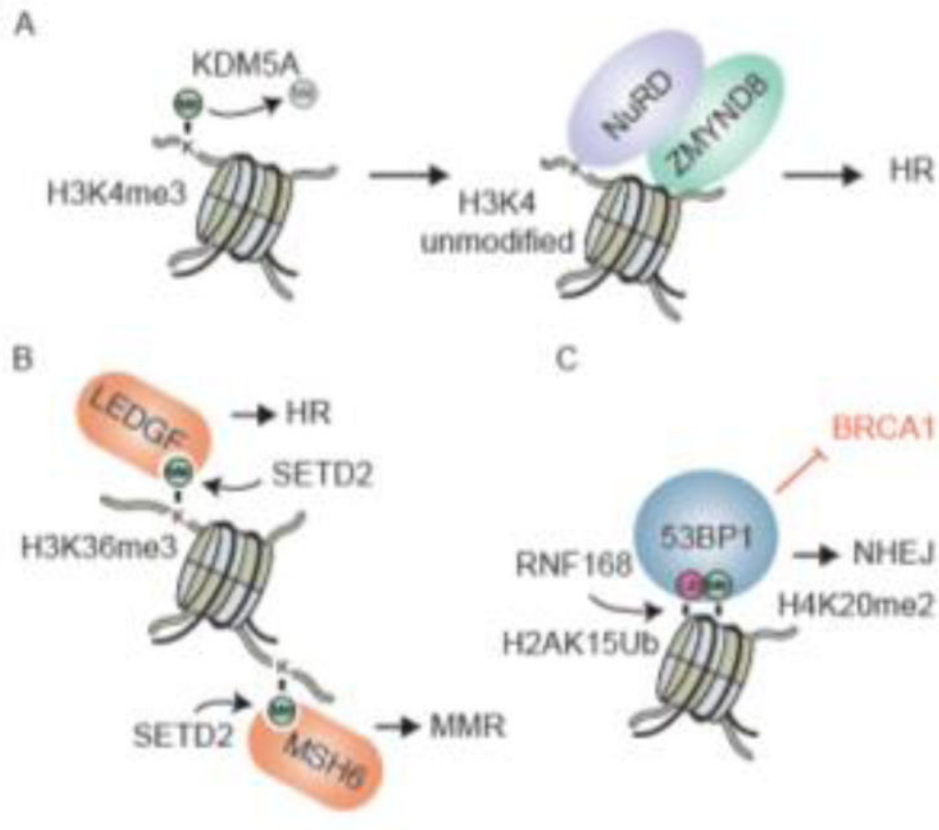
Fig. 3.
Histone methylation-dependent DDR mechanisms. (A) KDM5A-mediated H3K4me3 demethylation is required for the DDR pathway regulated by the ZMYND8-NuRD complex to promote homologous recombination (HR) repair. (B) Trimethylation on H3K36 (H3K36me3) catalyzed by SETD2 provides a binding site for LEDGF and MSH6, which promote HR and mismatch repair (MMR) respectively. (C) Bivalent recognition of H2AK15Ub and H4K20me2 by 53BP1 facilitates non-homologous end-joining (NHEJ) and blocks BRCA1 to limit HR repair.

Table 1

Histone methylation enzymes involved in the DDR in mammalian cells

	Nomenclature	Symbol/Alias	Histone targets upon DDR	Damage recruitment	DDR function	References
KMTs	KMT1A	SUV39H1	H3K9me3	R.E., Laser	HR; Genome stability	[85–87, 182]
	KMT1B	SUV39H2	H3K9me3, H2AXK134me2		HR; Genome stability; γH2AX maintenance	[85, 87, 134, 135, 182]
	KMT1C	G9a, EHMT2	H3K9me1/2	Degradation	DDR-induced SASP	[91, 183]
	KMT1D	GLP, EHMT1	H3K9me1/2	Degradation	DDR-induced SASP	[91]
	KMT1E	SETDB1	H3K9me3	Laser, R.E.	HR	[87]
	KMT2D	MLL4			Block DNA damage induced differentiation	[83]
	KMT3A	SETD2	H3K36me3		MMR, HR	[103–105, 112, 113]
	KMT3G	MMSET, WHSC1, NSD2	H4K20me2/3	IR, Laser	53BP1 recruitment	[124, 125, 128]
	KMT4	DOT1L	H3K79me2		53BP1 recruitment	[41, 119]
	KMT5A	PR-Set7, SET8, SETD8	H4K20me1	Laser	53BP1 recruitment, S-phase checkpoint	[39, 126, 184]
	KMT5B	Suv4-20h1	H4K20me2/3		DSB repair; CSR	[133]
	KMT5C	Suv4-20h2	H4K20me2/3		DSB repair; CSR	[133]
	KMT6	EZH2	H3K27me3	Laser, R.E., H_2O_2	Form repressive chromatin	[95–98]
	KMT8A	PRDM2, RIZ1	H3K9me2	Laser	HR	[88]
	SETMAR	Metnase	H3K36me2	R.E.	NHEJ	[107, 108]
	Other KMTs: KMT1F (SETDB2), KMT2A (MLL), KMT2B (MLL2), KMT2C (MLL3), KMT2E (MLL5), KMT2F (SETD1A), KMT2G (SETD1B), KMT2H (ASH1L), KMT3B (NSD1), KMT3C (SMYD2), KMT3D (SMYD1), KMT3E (SMYD3), KMT3F (WHSCL1L, NSD3), KMT6B (EZH1), KMT7 (SET7, SET9, SETD9), KMT8B (PRDM9), KMT8C (PRDM6), KMT8D (PRDM8), KMT8E (PRDM3), KMT8F (PRDM16)					
PRMTs	PRMT7		H2AR3me2, H4R3me2		Inhibition of repair gene expression	[136, 185]
	Other PRMTs: PRMT1, PRMT2, PRMT3, CARM1 (PRMT4), PRMT5, PRMT6, PRMT7, PRMT8, PRMT9					
KDMs	KMT1A	LSD1	H3K4me2	Laser, R.E.	DSB repair	[47, 48]
	KDM2A	JHDM1A, FBXL11	H3K36me2	Excluded	Promote MRN binding	[77, 186]
	KDM3C	JMJD1C		Laser	MDC1 demethylation	[109]
	KDM4A	JMJD2A, JHDM3A		Degradation	Expose H4K20me2 for 53BP1 binding	[143]
	KDM4B	JMJD2B	H3K9me2/3	Laser	Overexpression increase DSB repair	[110]
	KDM4D	JMJD2D	H3K9me2/3	Laser	DSB repair	[92]
						[92, 93]

Nomenclature	Symbol/Alias	Histone targets upon DDR	Damage recruitment	DDR function	References
KDM5A	JARID1A, RBP2	H3K4me3	Laser	HR, Transcription repression	[78, 187]
KDM5B	JARID1B, PLU1	H3K4me3	R.E.	HR, NHEJ	[76]
KDM5C	JARID1C, SMCX	H3K4me3		Transcription repression	[79]
Other KDMs: KDM1B (LSD2), KDM2B (FBXL10, JHDM1B), KDM3A (JHDM2A, JMJD1A), KDM3B (JHDM2B), KDM4C (JMJD2C, GASC1), KDM5D (JARID1D), KDM6A (UTX), KDM6B (JMJD3), KDM7A (JHDM1D), KDM7B (PHF8), KDM7C (PHF2), KDM8 (JMJD5), NO66					[46, 52, 69]

Mammalian histone methyltransferases (including both KMTs and PRMTs) and demethylases (KDMs) are listed. DNA damage affects reported for specific histone residues and DDR pathways are provided for each enzyme. Abbreviations: KMTs - Histone lysine methyltransferases; PRMTs - Protein arginine methyltransferases; KDMs - Histone lysine demethylases; R.E. - Restriction enzyme; IR - Ionizing radiation; MMR - Mismatch repair; HR - Homologous recombination; NHEJ - Non-homologous end-joining; CSR - Class-switch recombination; SASP - Senescence-associated secretory phenotype.