Role of histone methylation in maintenance of genome integrity

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Abstract

Packaging of the eukaryotic DNA genome with histone and other proteins forms a chromatin structure that regulates the outcome of all DNA mediated processes. The cellular pathways that ensure genomic stability detect and repair DNA damage through mechanisms which are critically dependent upon chromatin structures established by histones and, particularly, transient histone post-translational modifications . Though subject to a range of modifications, histone methylation is especially crucial for DNA damage repair as the methylated histones often form platforms for subsequent repair protein binding at damaged sites. In this review, we highlight and discuss how histone methylation impacts the maintenance of genome integrity through effects related to DNA repair and repair pathway choice.

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Introduction

The packaging of eukaryotic DNA with histone proteins forms the fundamental unit of chromatin called the nucleosome. Nucleosomes contains 146 base pairs of DNA wrapped around a histone octamer containing two each of the H2A, H2B, H3 and H4 histones (1,2). Apart from histone, non-histone proteins also bind to the DNA and alter the chromatin structure. The compaction of large DNA segments into chromatin imposes a barrier to proteins that need access to DNA template for processes like transcription, replication, recombination and repair (2). Chromatin structure can be modulated by various mechanisms including ATP-dependent chromatin remodeling proteins, histone variant exchange and histone post-translational modifications to ensure access by various proteins to the DNA (2). The eukaryotic genome is constantly challenged by various exogenous and endogenous DNA damaging agents like reactive oxygen intermediates, UV light, ionizing radiation or other chemical agents that cause various types of DNA breaks (3). Accurate repair of damaged DNA is essential for genomic stability. Failure to repair DNA breaks can lead to various diseases including cancer, ageing and neurodegenerative disorders (3,4). Therefore, it is important that cells identify the breaks and initiate and activate processes to repair the damaged DNA (5,6). Cells respond to breaks in the genome by activating a network of pathways, collectively called the DNA damage response (DDR), that detect the breaks and generate an appropriate protective response. One of the most deleterious type of DNA damage are DNA double-strand breaks (DSBs) (7-10). Two important pathways exist to repair DSBs: non-homologous end-joining (NHEJ) and (homologous recombination (HR) (11). NHEJ utilizes an error prone, direct religation repair mechanism and is active in G0 and G1 phase of the cell cycle. In contrast, HR uses a homologous DNA sequence as a repair template, is highly accurate and is

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mostly active in the S and G2 phase of cell cycle (12,13). Chromatin based mechanisms play a very crucial role in DNA damage repair by marking the damage sites and initiating signalling cascade to coordinate repair process.

Histone proteins undergo various post-translational modifications (PTMs) like phosphorylation, acetylation, methylation, ubiquitylation and sumoylation (1,2). These modifications influence chromatin structure by altering histone DNA interactions and also by acting as docking sites for various proteins to regulate essential aspects of DNA dependent transactions (1,2). In response to DNA damage, histone modifications are critical for DNA break repair and cell survival (14). Histone modifications help in sensing the DNA damage, facilitate recruitment of repair factors to the break site and re-establish a normal chromatin structure after repair (14). An especially prominent and widely studied modification with respect to transcription and DNA repair is histone methylation. Additional cellular processes regulated by histone methylation include X-chromosome inactivation, cell differentiation, and heterochromatin formation (15). Accumulating evidence suggests that histone methylation is important for repair of DSBs and also contributes to repair pathway choice. Several lysine residues in histones are modified in response to DNA damage, these include histone H3K4, H3K9, H3K27, H3K36, H3K79 and histone H4 lysine 20 (Table 1). In this review, we will focus on how histone methylations regulate the DNA damage response.

Histone H4K20 Methylation in DNA repair

Histone H4 lysine 20 methylation is the only reported methylation site on H4 having a role in maintaining genome integrity upon DNA damage (16). H4K20 methylation is catalyzed by several histone methyltransferases: PR-Set7/Set8/KMT5A is responsible for monomethylation of H4K20, while H4K20me2/3 methylation is catalyzed by SUV4-

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20h1/2 (16). H4K20 methylation levels do not change upon DNA damage, however the preexisting H4K20me becomes exposed and assists repair protein recruitment to the damage site (17,18). H4K20 methylation can be regulated by Epidermal Growth Factor Receptor (EGFR) which phosphorylates H4Y72 and leads to increased H4K20 methylation levels (19) by increasing the interaction of histone H4 with Set8 and Suv420H methyltransferase. (19). An H4Y72F mutant displays reduced DNA repair activity upon IR induced DNA damage (19). H4K20 methylation plays a prominent role in NHEJ by serving as a binding site for 53BP1 at damage sites, which then stimulates a downstream cascade involving DSB responsive proteins and checkpoint signaling proteins (20,21). 53BP1 binds to methylated H4K20 via its tandem tudor domain (22). In fission yeast Set9 meditated methylation of H4K20 localizes Crb2 (53BP1 ortholog) to DNA damage sites (18,23). In normal cells, methyl-binding proteins, L3MBTL1 (Lethal (3) malignant brain tumor like protein 1) and JMJD2A/KDM4A bind to H4K20me2 and thus prevents binding of 53BP1 in the absence of DNA damage (24-28). Binding of 53BP1 to H4K20 methylated chromatin is also obstructed by neighboring H4K16 acetylation, conversely deacetylation of H4K16 increased binding of 53BP1-H4K20me2 at DSB sites (29). L3MBTL1 and JMJD2A are released from H4K20me2 upon induction of DNA damage through ATM mediated recruitment of MDC1 (Mediator of DNA damage checkpoint 1) and phosphorylation of MDC1 at Ser 139. This leads to accumulation of RNF8 and RNF168 at DSBs which causes ubiquitinoylation of L3MBTL1 and JMJD2A (30-32). The removal of ubiquitinylated L3MDTL1 is mediated by VCP (ATPase valosin containing protein) and NPL4 (Nuclear Protein Localizing Cofactor Protein 4), while ubiquitinylated JMJD2A undergo proteosome-mediated degradation (30). Thus, upon DNA damage exposed H4K20me2 becomes available for 53BP1 binding to initiate NHEJ (31,32). 53BP1

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recruits downstream effector proteins, RIF1 and MAD12 that inhibits BRCA1 protein binding to promote NHEJ over HR in G1 phase of cell cycle (Figure 1) (33-35). In response to DNA damage, 53BP1 and BRCA1 competition regulates repair pathway choice between NHEJ and HR. Cells lacking BRCA1 have impaired HR repair and BRCA1deficient mice are embryonically lethal, a phenotype that can be rescued by loss of 53BP1. These findings indicate that in absence of BRCA1, 53BP1 blocks HR repair (36-38). The data also suggest that proper regulation of pathway choice is critical for maintenance of genome stability and H4K20 methylation plays an essential role in deciding the repair pathway choice. TIP60 mediated acetylation of H4K16 and H2AK15 in response to DNA damage block 53BP1 binding and favor HR. Acetylated H4K16 prevents 53BP1 binding to the H4K20 methylated residue due to steric hindrance (39). Acetylation of H2AK15 by TIP60 prevents its ubiquitylation, which is also a recognition site for 53BP1 (17,22,40). These studies suggest that multiple proteins and critical histone modifications regulate the DNA damage response through H4K20 methylation.

Histone H3K4 methylation in DNA repair

Methylation of histone H3 at lysine 4 by Set1p histone methyltransferase is associated with transcriptional activation and a proper response to DNA damage In budding yeast. (41-43).. Cells lacking Set1 or a H3K4 mutation have significantly compromised DSBs repair by the NHEJ pathway and decreased survival in the presence of replication stresses (44). Set1 binding and H3K4me3 levels are enriched around DSB break sites. It has also been observed that H3K4 demethylation by KDM5B at damage sites is important for the repair of DNA lesions in human cells (45,46). Demethylation is thought to modulate the chromatin structure from a transcriptionally favored state to a

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chromatin state that facilitates DNA repair. KDM5B has been reported to be enriched at I-SceI- induced DSB sites in a PARP1 and macroH2A1.1 dependent manner (47). Further, catalytically dead mutations of KDM5B,, or KDM5B loss, abolish BRCA1 and Ku70 recruitment to damage sites and leads to defective HR and NEHJ repair (47). Another demethylase, KDM5A demethylates H3K4me3 and facilitates the recruitment of the chromatin remodeling complex ZMYND8-NuRD to DNA damage sites (48). ZMYND8-NuRD represses transcription around the DNA double strand break site. Cells lacking KDM5A manifest impaired transcriptional repression and HR repair at DSBs similar to that observed after ZMYND8-NuRD loss (49). In addition to KDM5A and KDM5B, the KDM5C H3K4me3 demethylase has a role in the DDR in response to replication stress induced by alkylating agents like methyl methanesulfonate (MMS). After simulation, KDM5C is recruited to chromatin where it demethylates H3K4me3 in order to maintain the repressed chromatin state (50). Thus different demethylases play different roles depending upon the nature of the DNA damage.

H3K36 methylation in the DNA damage response

Methylated H3K36 is highly enriched within the coding regions of actively transcribed genes as part of transcription elongation. H3K36 methylation is also involved in splicing and suppression of cryptic intragenic transcription (51,52). Several enzymes have been shown to methylate H3K36, but SETD2 (KMT3A) is the only methyltransferase which trimethylates H3K36 (49,51). Several reports have linked H3K36 methylation with the DNA damage response that occurs preferentially at breaks in transcriptionally active regions of the genome (53). Depletion of SETD2 leads to decreased phosphorylation of ATM and p53, defective DNA end resection

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and loss of recruitment of RPA and RAD51 to damaged sites and reduced HR efficiency (53-55). H3K36 methylation is important for HR repair as it acts as a docking site for the PWWP methyl binding domain of LEDGF (Lens epithelium–derived growth factor) (56). Upon DNA damage, LEDGF binding to H3K36me3 enables the recruitment of CtIP (C-terminal binding protein interacting protein, a DNA damage response factor), to DNA DSBs sites and promotes the CtIP dependent resection steps associated with DSB repair by HR (56). Depletion of SETD2 impairs LEDGF binding to chromatin which hinders CtIP recruitment resulting in defective end-resection and reduction in ssDNA binding proteins RPA and RAD51 at the damage sites (53,56,57). Overexpression of the H3K36me3 demethylase KDM4A (JMJD2A or JHDM3A) decreases HR efficiency (54). In contrast to H3K36 trimethylation which favours HR, dimethylation of H3K36 promotes NHEJ (58,59). IR induced DSBs cause enrichment of H3K36me2 around the break sites and binding of NHEJ proteins. Metnase (SETMAR) is recruited to damage sites and mediates demethylation of H3K36 around the break site (60,61). Dimethylated H3K36 leads to recruitment and stabilization of Ku70/Ku80, PHRF1 (PHD and ring finger domain 1) and NBS1 thereby promoting DSB repair by the NHEJ pathway (62). Depletion of Metnase or H3K36me2 depletion by demethylase KDM2A knockdown inhibits the NHEJ repair pathway. Further, mutation of H3K36 to H3R36 or H3A36 results in marked decrease in the recruitment of Ku70 and NBS1 to DSBs, indicating that H3K36me2 is essential for assembly of repair proteins at DSBs and for efficient DSB repair (58,62). While these findings indicate that H3K36me2 and H3K36me3 methylation decide the repair of DSBs either by HR or NHEJ (Figure 2), the precise molecular factors that govern the activation of these repair pathways are not fully known.

Histone H3K79 methylation in DNA repair

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Unlike most histone methylations that occur on the histone tails, H3K79 methylation occurs within the globular domain of histone H3 (1,63). H3K79 is methylated by an evolutionarily conserved non-SET containing histone methyltransferase called Disruptor of telomeric silencing-1 (hDot1) (1,64). Dot1 was initially discovered as a gene whose overexpression causes silencing defects at telomeres in budding yeast. H3K79 methylation plays a role in transcription, telomeric silencing, and cell cycle regulation (1,65). Dot1 has become an attractive therapeutic target in MLL-induced leukemia, where chromosomal translocations fuse Dot1 with several proteins (66) . These fusion proteins mistarget Dot1 to ectopic sites such as Hox gene clusters and leads to hypermethylation and transcriptional activation of Hox gene clusters. This constitutive HOX expression has been found to drive leukemogenesis (66,67). Apart from these aberrant functions, numerous studies across species have linked Dot1 mediated H3K79 methylation with DNA damage repair where it provides a binding site for 53BP1 repair protein in humans, and its ortholog Rad9 in yeast, to DNA damage sites important for checkpoint activation (68). Both 53BP1/Rad9 bind to methylated H3K79 chromatin through their tudor domains. Depletion of Dot1 or mutation of H3K79 impairs recruitment of 53BP1 or Rad9 to DNA DSB sites (69). Similarly, mutations in the tudor domain of 53BP1 or Rad9 abolishes their recruitment to DSBs (68,70). Recruitment of 53BP1 to DSBs by H3K79me3 drives NHEJ in G1/G2 phases of cell cycle (60). In budding yeast, recruitment of Rad9 by H3K79me3 is important to G2 phase DNA damage repair by limiting ssDNA production during non-homologous end joining (71). H3K79 methylation has also been shown to be critical for nucleotide excision repair (NER) in response to UV-induced DNA damage, as cells lacking Dot1 or with mutated H3K79 are UV hypersensitive (72). H3K79 methylation might help in recruiting XPC, which in turn enhances efficient removal of UV photoproducts.

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Cross-talk between H3K9 methylation, ATM and TIP60

Histone H3 methylation at lysine 9 (H3K9me3) is mainly associated with heterochromatin mediated gene silencing (73,74). H3K9 methylation is catalysed by histone methyltransferase suppressor of variegation 3–9 homolog 1 (Suv39H1) or its homolog Suv39H2 (75-77). Suv39H1 and Suv39H2 are recruited to DNA DSBs leading to increased H3K9 methylation around the break sites. H3K9 methylation sites are then recognized by the histone acetyltransferase TIP60 through its chromodomain (77). The interaction of TIP60 with H3K9me3 stimulates its HAT activity which increases acetylation of H4, H2A and ATM and its increased kinase activity subsequently initiates downstream ATM signalling and HR repair (39,77). Methylation of H3K9 also helps increase binding of a histone methyltransferase SUV39H1, KAP1 and HP1 complex to DSBs which furthers spreading of H3K9 methylation, more TIP60 recruitment and additional TIP60 mediated ATM activation. ATM activation ultimately releases SUV39H1-KAP1-HP1 complex from the break sites by phosphorylating KAP1 (76). Acetylation of H4 and H2A by TIP60 around break sites prevents 53BP1 binding which would have favoured NHEJ repair by preventing DNA end-resection (30,39). Thus, TIP60 promotes HR by preventing 53BP1 binding (Figure 3). Depletion of SUV39H1 or H3K9 mutation decreases TIP60 mediated histone acetylation around DSB sites and hence impairs HR repair (76). Histone demethylases l(KDM4B (JMJD2B) and KDM4D (JMJD2D)) specific to H3K9me3 have also been shown to play role in DDR (78,79). PARP1, a poly ADP-ribose polymerase recruits these KDMs to the DNA damage sites. Upon DNA damage, KDM4D is PARylated by PARP1 and (78) and depletion of KDM4D impairs association of ATM with chromatin and inhibits ATM dependent signalling and phosphorylation of H2AX, KAP1 and CHK2 (78). Cells

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depleted of KDM4D show reduced binding of Rad51 and 53BP1 and defects in both the HR and NHEJ pathways. The role of H3K9me3 demethylases in DNA repair was further supported by the fact that catalically dead KDM4D mutant cells have HR defects similar to those in cells lacking KDM4D. However, the mechanism coordinating damage induced H3K9me3 demethylation with H3K9 methyltransferases is not clear nor is the precise mechanism by which the same residue can regulate pathway choice (49,78).

Conclusions and Future Perspectives

As part of the cellular response to DNA damage, a wide range of histone PTMs (phosphorylation, ubiquitylation, acetylation and methylation) have been shown to play important roles in generating and regulating DDRs. In this review, we discussed the role of specific histone methylation sites/enzymes in DNA DSB repair and also how they regulate pathway choice. Many histone methyltransferases and demethylases are recruited to chromatin in response to damage and change the local chromatin structure to facilitate repair protein recruitment. However, there are still several gaps that need to be addressed to fully understand the role of histone methylation in DNA repair. Several histone methyltransferases and demethyltransferases target the same histone site, how is the activity of these enzymes regulated or their targeting to same genomic loci. Sometimes the same modification can regulate both HR and NHEJ depending on the level of modification, knowing the whole reporter of methyl readers would shed light on how these modifications regulate different repair pathways. It has also been shown that both histone methyltransferases and demethylases against a specific methylations plays a role in DNA repair, but how the activities of these two

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opposing enzymes regulating same outcome in context to DNA repair needs to be elucidiated further. Also mutations of various methylation sites or mis-regulation of methyltransferases or demethylases and failure to repair damaged DNA in various diseases needs to be further pursued. The nature of the chromatin state before and after DNA damage, how that structure varies between different genomic loci and the influence of specific types of. DNA damage on repair outcomes are all challenging questions that need to be addressed.

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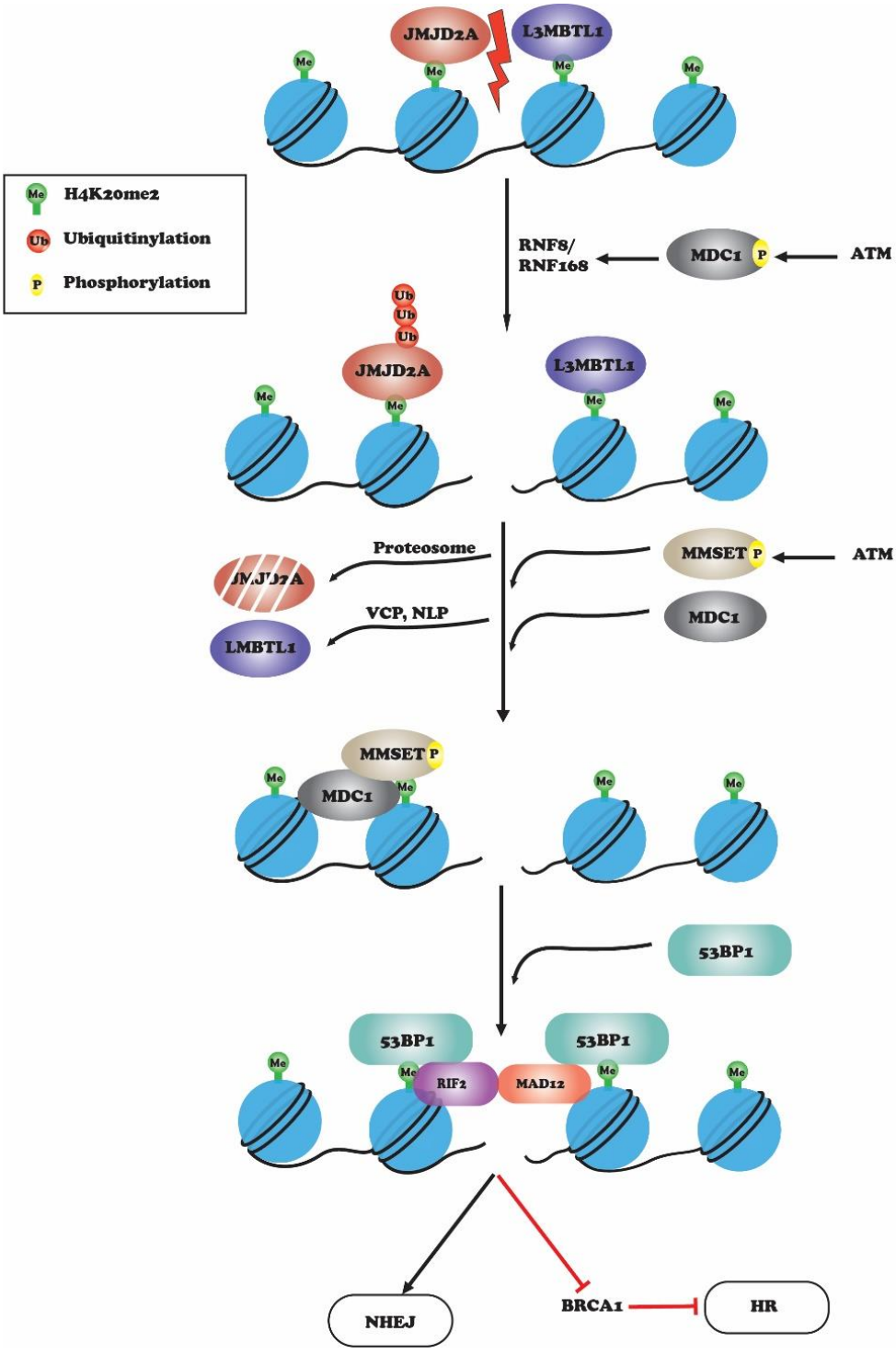

Figure 1: Upon DNA damage, L3MBTL1 and JMJD2A are released from H4K20me2 through ATM mediated recruitment of MDC1 and phosphorylation of MDC1 at Ser 139.This leads to accumulation of RNF8 and RNF168 at DSBs which causes ubiquitinoylation and degradation of JMJD2A by proteosome-mediated degradation and removal of L3MBTL1 by VCP (ATPase valosin containing protein) and NPL4 (Nuclear Protein Localizing Cofactor Protein 4). Thus, upon DNA damage exposed H4K20me2 becomes available for 53BP1 binding to initiate NHEJ. 53BP1 recruits downstream effector proteins, RIF1 and MAD12 that inhibits BRCA1 protein binding to promote NHEJ over HR in G1 phase of cell cycle.

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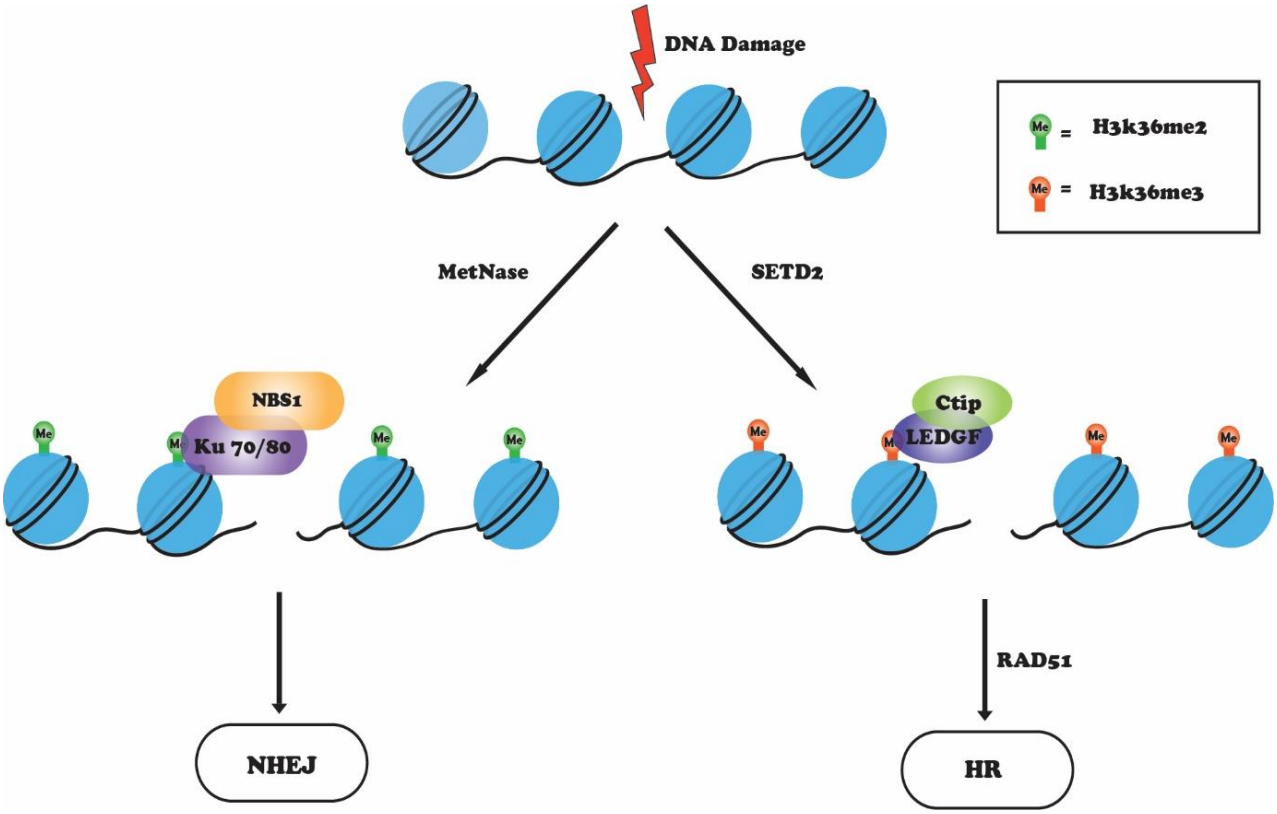

Figure 2: Upon DNA damage, Metnase catalyses H3K36me2 which recruits Ku70-NBS1 complex to repair DNA damage via NHEJ pathway. While, H3K36me3 catalysed by SETD2 favours HR pathway by recruiting LEDGF-CtIP complex. This is followed by RAD51 recruitment and in turn HR repair.

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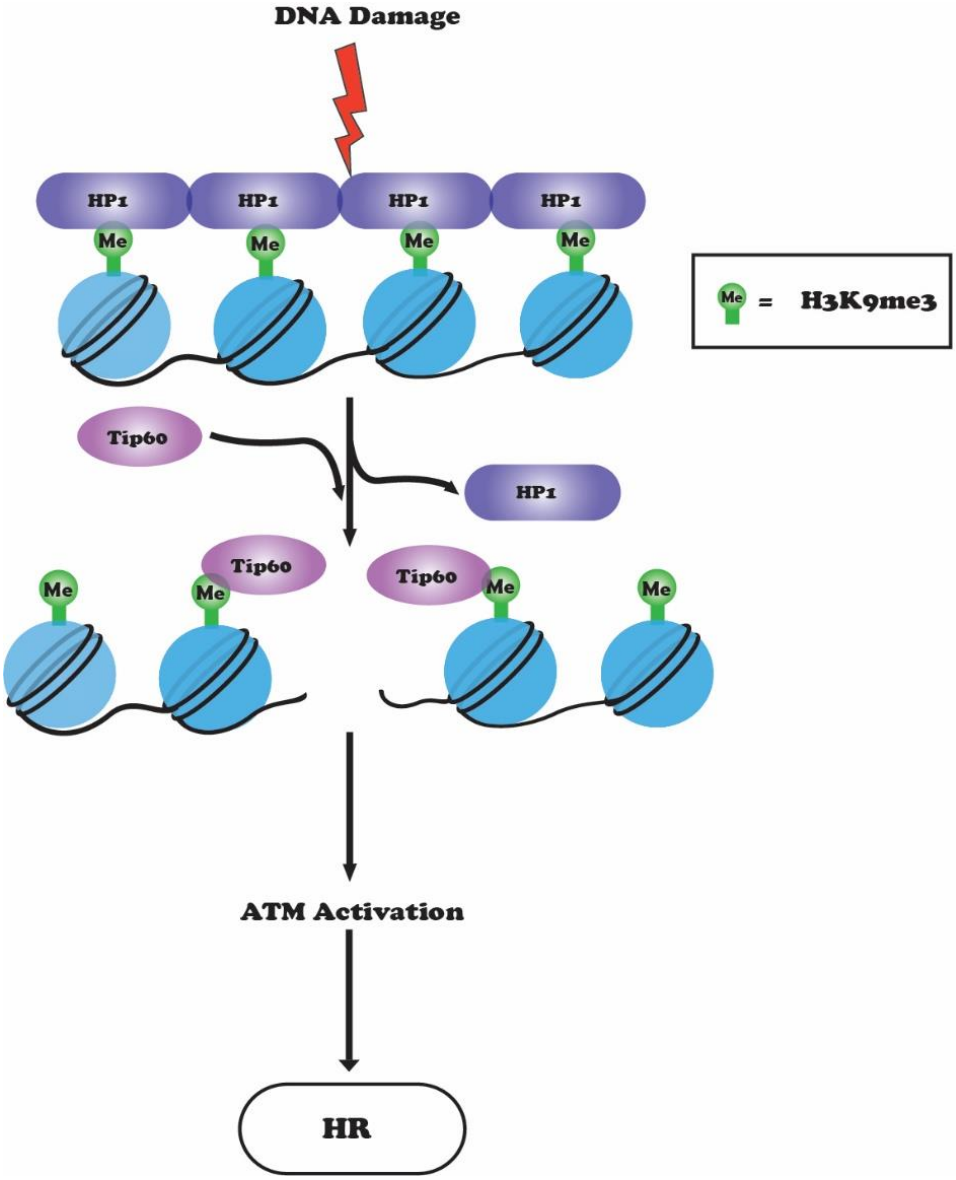

Figure 3: In response to DNA damage, HP1 is displaced from the H3K9me3 site allowing TIP60 to interact with H3K9me3 via its chromodomain. The interaction of TIP60 with H3K9me3 stimulates its HAT activity which leads to acetylation of ATM and subsequent activation of its kinase activity, downstream ATM signalling and HR-mediated repair.

References

1. Farooq, Z., Banday, S., Pandita, T.K. and Altaf, M. (2016) The many faces of histone H3K79 methylation. Mutat Res Rev Mutat Res, 768, 46-52.
2. Altaf, M., Saksouk, N. and Cote, J. (2007) Histone modifications in response to DNA damage. Mutat Res, 618, 81-90.
3. Tubbs, A. and Nussenzweig, A. (2017) Endogenous DNA Damage as a Source of Genomic Instability in Cancer. Cell, 168, 644-656.
4. Ganai, S.A., Rashid, R., Abdullah, E. and Altaf, M. (2017) Plant Derived Inhibitor Sulforaphane in Combinatorial Therapy Against Therapeutically Challenging Pancreatic Cancer. Anticancer Agents Med Chem, 17, 365-373.
5. Marteijn, J.A., Lans, H., Vermeulen, W. and Hoeijmakers, J.H. (2014) Understanding nucleotide excision repair and its roles in cancer and ageing. Nat Rev Mol Cell Biol, 15, 465-481.
6. Jiricny, J. (2006) The multifaceted mismatch-repair system. Nat Rev Mol Cell Biol, 7, 335-346.
7. Helleday, T., Lo, J., van Gent, D.C. and Engelward, B.P. (2007) DNA double-strand break repair: from mechanistic understanding to cancer treatment. DNA Repair (Amst), 6, 923-935.
8. Khanna, K.K. and Jackson, S.P. (2001) DNA double-strand breaks: signaling, repair and the cancer connection. Nat Genet, 27, 247-254.
9. Haber, J.E. (2000) Partners and pathwaysrepairing a double-strand break. Trends Genet, 16, 259-264.
10. Kanaar, R., Hoeijmakers, J.H. and van Gent, D.C. (1998) Molecular mechanisms of DNA double strand break repair. Trends Cell Biol, 8, 483-489.
11. Huertas, P. (2010) DNA resection in eukaryotes: deciding how to fix the break. Nat Struct Mol Biol, 17, 11-16.
12. Shibata, A. (2017) Regulation of repair pathway choice at two-ended DNA double-strand breaks. Mutat Res, 803-805, 51-55.
13. Symington, L.S. and Gautier, J. (2011) Double-strand break end resection and repair pathway choice. Annu Rev Genet, 45, 247-271.
14. Van, H.T. and Santos, M.A. (2018) Histone modifications and the DNA double-strand break response. Cell Cycle, 17, 2399-2410.
15. Greer, E.L. and Shi, Y. (2012) Histone methylation: a dynamic mark in health, disease and inheritance. Nat Rev Genet, 13, 343-357.
16. Pei, H., Zhang, L., Luo, K., Qin, Y., Chesi, M., Fei, F., Bergsagel, P.L., Wang, L., You, Z. and Lou, Z. (2011) MMSET regulates histone H4K20 methylation and 53BP1 accumulation at DNA damage sites. Nature, 470, 124-128.
17. Botuyan, M.V., Lee, J., Ward, I.M., Kim, J.E., Thompson, J.R., Chen, J. and Mer, G. (2006) Structural basis for the methylation state-specific recognition of histone H4-K20 by 53BP1 and Crb2 in DNA repair. Cell, 127, 1361-1373.
18. Sanders, S.L., Portoso, M., Mata, J., Bahler, J., Allshire, R.C. and Kouzarides, T. (2004) Methylation of histone H4 lysine 20 controls recruitment of Crb2 to sites of DNA damage. Cell, 119, 603-614.
19. Chou, R.H., Wang, Y.N., Hsieh, Y.H., Li, L.Y., Xia, W., Chang, W.C., Chang, L.C., Cheng, C.C., Lai, C.C., Hsu, J.L. et al. (2014) EGFR modulates DNA synthesis and repair through Tyr phosphorylation of histone H4. Dev Cell, 30, 224-237.

20. Panier, S. and Boulton, S.J. (2014) Double-strand break repair: 53BP1 comes into focus. Nat Rev Mol Cell Biol, 15, 7-18.
21. Zimmermann, M. and de Lange, T. (2014) 53BP1: pro choice in DNA repair. Trends Cell Biol, 24, 108-117.
22. Huyen, Y., Zgheib, O., Ditullio, R.A., Jr., Gorgoulis, V.G., Zacharatos, P., Petty, T.J., Sheston, E.A., Mellert, H.S., Stavridi, E.S. and Halazonetis, T.D. (2004) Methylated lysine 79 of histone H3 targets 53BP1 to DNA double-strand breaks. Nature, 432, 406-411.
23. Du, L.L., Nakamura, T.M. and Russell, P. (2006) Histone modification-dependent and -independent pathways for recruitment of checkpoint protein Crb2 to double-strand breaks. Genes Dev, 20, 1583-1596.
24. Trojer, P., Zhang, J., Yonezawa, M., Schmidt, A., Zheng, H., Jenuwein, T. and Reinberg, D. (2009) Dynamic Histone H1 Isotype 4 Methylation and Demethylation by Histone Lysine Methyltransferase G9a/KMT1C and the Jumonji Domain-containing JMJD2/KDM4 Proteins. J Biol Chem, 284, 8395-8405.
25. Lee, J., Thompson, J.R., Botuyan, M.V. and Mer, G. (2008) Distinct binding modes specify the recognition of methylated histones H3K4 and H4K20 by JMJD2A-tudor. Nat Struct Mol Biol, 15, 109-111.
26. Li, H., Fischle, W., Wang, W., Duncan, E.M., Liang, L., Murakami-Ishibe, S., Allis, C.D. and Patel, D.J. (2007) Structural basis for lower lysine methylation state-specific readout by MBT repeats of L3MBTL1 and an engineered PHD finger. Mol Cell, 28, 677-691.
27. Min, J., Allali-Hassani, A., Nady, N., Qi, C., Ouyang, H., Liu, Y., MacKenzie, F., Vedadi, M. and Arrowsmith, C.H. (2007) L3MBTL1 recognition of mono- and dimethylated histones. Nat Struct Mol Biol, 14, 1229-1230.
28. Kim, J., Daniel, J., Espejo, A., Lake, A., Krishna, M., Xia, L., Zhang, Y. and Bedford, M.T. (2006) Tudor, MBT and chromo domains gauge the degree of lysine methylation. EMBO Rep, 7, 397-403.
29. Hsiao, K.Y. and Mizzen, C.A. (2013) Histone H4 deacetylation facilitates 53BP1 DNA damage signaling and double-strand break repair. J Mol Cell Biol, 5, 157-165.
30. Jacquet, K., Fradet-Turcotte, A., Avvakumov, N., Lambert, J.P., Roques, C., Pandita, R.K., Paquet, E., Herst, P., Gingras, A.C., Pandita, T.K. et al. (2016) The TIP60 Complex Regulates Bivalent Chromatin Recognition by 53BP1 through Direct H4K20me Binding and H2AK15 Acetylation. Mol Cell, 62, 409-421.
31. Mallette, F.A., Mattiroli, F., Cui, G., Young, L.C., Hendzel, M.J., Mer, G., Sixma, T.K. and Richard, S. (2012) RNF8- and RNF168-dependent degradation of KDM4A/JMJD2A triggers 53BP1 recruitment to DNA damage sites. EMBO J, 31, 1865-1878.
32. Acs, K., Luijsterburg, M.S., Ackermann, L., Salomons, F.A., Hoppe, T. and Dantuma, N.P. (2011) The AAA-ATPase VCP/p97 promotes 53BP1 recruitment by removing L3MBTL1 from DNA double-strand breaks. Nat Struct Mol Biol, 18, 1345-1350.
33. Zhang, H., Liu, H., Chen, Y., Yang, X., Wang, P., Liu, T., Deng, M., Qin, B., Correia, C., Lee, S. et al. (2016) A cell cycle-dependent BRCA1-UHRF1 cascade regulates DNA double-strand break repair pathway choice. Nat Commun, 7, 10201.

34. Boersma, V., Moatti, N., Segura-Bayona, S., Peuscher, M.H., van der Torre, J., Wevers, B.A., Orthwein, A., Durocher, D. and Jacobs, J.J.L. (2015) MAD2L2 controls DNA repair at telomeres and DNA breaks by inhibiting 5' end resection. Nature, 521, 537-540.
35. Zimmermann, M., Lottersberger, F., Buonomo, S.B., Sfeir, A. and de Lange, T. (2013) 53BP1 regulates DSB repair using Rif1 to control 5' end resection. Science, 339, 700-704.
36. Daley, J.M. and Sung, P. (2014) 53BP1, BRCA1, and the choice between recombination and end joining at DNA double-strand breaks. Mol Cell Biol, 34, 1380-1388.
37. Chapman, J.R., Taylor, M.R. and Boulton, S.J. (2012) Playing the end game: DNA double-strand break repair pathway choice. Mol Cell, 47, 497-510.
38. Bunting, S.F., Callen, E., Wong, N., Chen, H.T., Polato, F., Gunn, A., Bothmer, A., Feldhahn, N., Fernandez-Capetillo, O., Cao, L. et al. (2010) 53BP1 inhibits homologous recombination in Brca1-deficient cells by blocking resection of DNA breaks. Cell, 141, 243-254.
39. Tang, J., Cho, N.W., Cui, G., Manion, E.M., Shanbhag, N.M., Botuyan, M.V., Mer, G. and Greenberg, R.A. (2013) Acetylation limits 53BP1 association with damaged chromatin to promote homologous recombination. Nat Struct Mol Biol, 20, 317-325.
40. Fradet-Turcotte, A., Canny, M.D., Escribano-Diaz, C., Orthwein, A., Leung, C.C., Huang, H., Landry, M.C., Kitevski-LeBlanc, J., Noordermeer, S.M., Sicheri, F. et al. (2013) 53BP1 is a reader of the DNA-damage-induced H2A Lys 15 ubiquitin mark. Nature, 499, 50-54.
41. Nagy, P.L., Griesenbeck, J., Kornberg, R.D. and Cleary, M.L. (2002) A trithorax-group complex purified from Saccharomyces cerevisiae is required for methylation of histone H3. Proc Natl Acad Sci U S A, 99, 90-94.
42. Roguev, A., Schaft, D., Shevchenko, A., Pijnappel, W.W., Wilm, M., Aasland, R. and Stewart, A.F. (2001) The Saccharomyces cerevisiae Set1 complex includes an Ash2 homologue and methylates histone 3 lysine 4. EMBO J, 20, 7137-7148.
43. Miller, T., Krogan, N.J., Dover, J., Erdjument-Bromage, H., Tempst, P., Johnston, M., Greenblatt, J.F. and Shilatifard, A. (2001) COMPASS: a complex of proteins associated with a trithorax-related SET domain protein. Proc Natl Acad Sci U S A, 98, 12902-12907.
44. Freitag, M. (2017) Histone Methylation by SET Domain Proteins in Fungi. Annu Rev Microbiol, 71, 413-439.
45. Li, L., Wang, L., Song, P., Geng, X., Liang, X., Zhou, M., Wang, Y., Chen, C., Jia, J. and Zeng, J. (2014) Critical role of histone demethylase RBP2 in human gastric cancer angiogenesis. Mol Cancer, 13, 81.
46. Mosammaparast, N., Kim, H., Laurent, B., Zhao, Y., Lim, H.J., Majid, M.C., Dango, S., Luo, Y., Hempel, K., Sowa, M.E. et al. (2013) The histone demethylase LSD1/KDM1A promotes the DNA damage response. J Cell Biol, 203, 457-470.
47. Li, X., Liu, L., Yang, S., Song, N., Zhou, X., Gao, J., Yu, N., Shan, L., Wang, Q., Liang, J. et al. (2014) Histone demethylase KDM5B is a key regulator of genome stability. Proc Natl Acad Sci U S A, 111, 7096-7101.
48. Gong, F., Clouaire, T., Aguirrebengoa, M., Legube, G. and Miller, K.M. (2017) Histone demethylase KDM5A regulates the ZMYND8-NuRD chromatin remodeler to promote DNA repair. J Cell Biol, 216, 1959-1974.

49. Gong, F. and Miller, K.M. (2019) Histone methylation and the DNA damage response. Mutat Res, 780, 37-47.
50. Hendriks, I.A. and Vertegaal, A.C. (2015) SUMO in the DNA damage response. Oncotarget, 6, 15734-15735.
51. Wagner, E.J. and Carpenter, P.B. (2012) Understanding the language of Lys36 methylation at histone H3. Nat Rev Mol Cell Biol, 13, 115-126.
52. Li, F., Mao, G., Tong, D., Huang, J., Gu, L., Yang, W. and Li, G.M. (2013) The histone mark H3K36me3 regulates human DNA mismatch repair through its interaction with MutSalpha. Cell, 153, 590-600.
53. Aymard, F., Bugler, B., Schmidt, C.K., Guillou, E., Caron, P., Briois, S., Iacovoni, J.S., Daburon, V., Miller, K.M., Jackson, S.P. et al. (2014) Transcriptionally active chromatin recruits homologous recombination at DNA double-strand breaks. Nat Struct Mol Biol, 21, 366-374.
54. Pfister, S.X., Ahrabi, S., Zalmas, L.P., Sarkar, S., Aymard, F., Bachrati, C.Z., Helleday, T., Legube, G., La Thangue, N.B., Porter, A.C. et al. (2014) SETD2-dependent histone H3K36 trimethylation is required for homologous recombination repair and genome stability. Cell Rep, 7, 2006-2018.
55. Carvalho, S., Vitor, A.C., Sridhara, S.C., Martins, F.B., Raposo, A.C., Desterro, J.M., Ferreira, J. and de Almeida, S.F. (2014) SETD2 is required for DNA double-strand break repair and activation of the p53-mediated checkpoint. Elife, 3, e02482.
56. Daugaard, M., Baude, A., Fugger, K., Povlsen, L.K., Beck, H., Sorensen, C.S., Petersen, N.H., Sorensen, P.H., Lukas, C., Bartek, J. et al. (2012) LEDGF (p75) promotes DNA-end resection and homologous recombination. Nat Struct Mol Biol, 19, 803-810.
57. Bannister, A.J., Schneider, R., Myers, F.A., Thorne, A.W., Crane-Robinson, C. and Kouzarides, T. (2005) Spatial distribution of di- and tri-methyl lysine 36 of histone H3 at active genes. J Biol Chem, 280, 17732-17736.
58. Fnu, S., Williamson, E.A., De Haro, L.P., Brenneman, M., Wray, J., Shaheen, M., Radhakrishnan, K., Lee, S.H., Nickoloff, J.A. and Hromas, R. (2011) Methylation of histone H3 lysine 36 enhances DNA repair by nonhomologous end-joining. Proc Natl Acad Sci U S A, 108, 540-545.
59. Strahl, B.D., Grant, P.A., Briggs, S.D., Sun, Z.W., Bone, J.R., Caldwell, J.A., Mollah, S., Cook, R.G., Shabanowitz, J., Hunt, D.F. et al. (2002) Set2 is a nucleosomal histone H3-selective methyltransferase that mediates transcriptional repression. Mol Cell Biol, 22, 1298-1306.
60. Wei, S., Li, C., Yin, Z., Wen, J., Meng, H., Xue, L. and Wang, J. (2018) Histone methylation in DNA repair and clinical practice: new findings during the past 5-years. J Cancer, 9, 2072-2081.
61. Hromas, R., Williamson, E.A., Fnu, S., Lee, Y.J., Park, S.J., Beck, B.D., You, J.S., Leitao, A., Nickoloff, J.A. and Lee, S.H. (2012) Chk1 phosphorylation of Metnase enhances DNA repair but inhibits replication fork restart. Oncogene, 31, 4245-4254.
62. Chang, C.F., Chu, P.C., Wu, P.Y., Yu, M.Y., Lee, J.Y., Tsai, M.D. and Chang, M.S. (2015) PHRF1 promotes genome integrity by modulating non-homologous end-joining. Cell Death Dis, 6, e1716.
63. Ng, H.H., Feng, Q., Wang, H., Erdjument-Bromage, H., Tempst, P., Zhang, Y. and Struhl, K. (2002) Lysine methylation within the globular domain of histone H3 by Dot1 is important for telomeric silencing and Sir protein association. Genes Dev, 16, 1518-1527.

64. Altaf, M., Utley, R.T., Lacoste, N., Tan, S., Briggs, S.D. and Cote, J. (2007) Interplay of chromatin modifiers on a short basic patch of histone H4 tail defines the boundary of telomeric heterochromatin. Mol Cell, 28, 1002-1014.
65. FitzGerald, J., Moureau, S., Drogaris, P., O'Connell, E., Abshiru, N., Verreault, A., Thibault, P., Grenon, M. and Lowndes, N.F. (2011) Regulation of the DNA damage response and gene expression by the Dot1L histone methyltransferase and the 53Bp1 tumour suppressor. PLoS One, 6, e14714.
66. Banday, S., Farooq, Z., Ganai, S.A. and Altaf, M. (2020) Therapeutic strategies against hDOT1L as a potential drug target in MLL-rearranged leukemias. Clin Epigenetics, 12, 73.
67. Okada, Y., Feng, Q., Lin, Y., Jiang, Q., Li, Y., Coffield, V.M., Su, L., Xu, G. and Zhang, Y. (2005) hDOT1L links histone methylation to leukemogenesis. Cell, 121, 167-178.
68. Nguyen, A.T. and Zhang, Y. (2011) The diverse functions of Dot1 and H3K79 methylation. Genes Dev, 25, 1345-1358.
69. Wysocki, R., Javaheri, A., Allard, S., Sha, F., Cote, J. and Kron, S.J. (2005) Role of Dot1-dependent histone H3 methylation in G1 and S phase DNA damage checkpoint functions of Rad9. Mol Cell Biol, 25, 8430-8443.
70. Usui, T. and Shinohara, A. (2021) Rad9, a 53BP1 Ortholog of Budding Yeast, Is Insensitive to Spo11-Induced Double-Strand Breaks During Meiosis. Front Cell Dev Biol, 9, 635383.
71. Wood, K., Tellier, M. and Murphy, S. (2018) DOT1L and H3K79 Methylation in Transcription and Genomic Stability. Biomolecules, 8.
72. Zhu, B., Chen, S., Wang, H., Yin, C., Han, C., Peng, C., Liu, Z., Wan, L., Zhang, X., Zhang, J. et al. (2018) The protective role of DOT1L in UV-induced melanomagenesis. Nat Commun, 9, 259.
73. Barski, A., Cuddapah, S., Cui, K., Roh, T.Y., Schones, D.E., Wang, Z., Wei, G., Chepelev, I. and Zhao, K. (2007) High-resolution profiling of histone methylations in the human genome. Cell, 129, 823-837.
74. Bannister, A.J., Zegerman, P., Partridge, J.F., Miska, E.A., Thomas, J.O., Allshire, R.C. and Kouzarides, T. (2001) Selective recognition of methylated lysine 9 on histone H3 by the HP1 chromo domain. Nature, 410, 120-124.
75. Alagoz, M., Katsuki, Y., Ogiwara, H., Ogi, T., Shibata, A., Kakarougkas, A. and Jeggo, P. (2015) SETDB1, HP1 and SUV39 promote repositioning of 53BP1 to extend resection during homologous recombination in G2 cells. Nucleic Acids Res, 43, 7931-7944.
76. Ayrapetov, M.K., Gursoy-Yuzugullu, O., Xu, C., Xu, Y. and Price, B.D. (2014) DNA double-strand breaks promote methylation of histone H3 on lysine 9 and transient formation of repressive chromatin. Proc Natl Acad Sci U S A, 111, 9169-9174.
77. Sun, Y., Jiang, X., Xu, Y., Ayrapetov, M.K., Moreau, L.A., Whetstine, J.R. and Price, B.D. (2009) Histone H3 methylation links DNA damage detection to activation of the tumour suppressor Tip60. Nat Cell Biol, 11, 1376-1382.
78. Khoury-Haddad, H., Guttmann-Raviv, N., Ipenberg, I., Huggins, D., Jeyasekharan, A.D. and Ayoub, N. (2014) PARP1-dependent recruitment of KDM4D histone demethylase to DNA damage sites promotes double-strand break repair. Proc Natl Acad Sci U S A, 111, E728-737.
79. Young, L.C., McDonald, D.W. and Hendzel, M.J. (2013) Kdm4b histone demethylase is a DNA damage response protein and confers a survival advantage following gamma-irradiation. J Biol Chem, 288, 21376-21388.

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