Published in final edited form as:

J Cancer Biol. 2020 ; 1(1): 10–15. doi:10.46439/cancerbiology.1.003.

Role of H3K9 demethylases in DNA double-strand break repair

Hee-Young Jeon^{1,2}, Arif Hussain^{2,3}, Jianfei Qi^{1,2,#}

¹Department of Biochemistry and Molecular Biology, University of Maryland, Baltimore, MD, USA

²Marlene and Stewart Greenebaum Comprehensive Cancer Center, Baltimore, MD, USA

³Baltimore VA Medical Center, Baltimore, MD, USA

Abstract

H3K9 demethylases can remove the repressive H3K9 methylation marks on histones to alter chromatin structure, gene transcription and epigenetic state of cells. By counteracting the function of H3K9 methyltransferases, H3K9 demethylases have been shown to play an important role in numerous biological processes, including diseases such as cancer. Recent evidence points to a key role for some H3K9 demethylases in the repair of DNA double-strand breaks (DSBs) via homologous recombination (HR) and/or non-homologous end joining (NHEJ) pathways. Mechanistically, H3K9 demethylases can upregulate the expression of DNA repair factors. They can also be recruited to the DNA damage sites and regulate the recruitment or function of DNA repair factors. Here, we will discuss the role and mechanisms of H3K9 demethylases in the regulation of DSB repair.

Keywords

H3K9; demethylation; histone demethylase; double-strand breaks; DNA damage repair; cancer; epigenetic

Introduction

Methylation of histone H3 at lysine 9 (H3K9me) and the subsequent binding of heterochromatin protein 1 (HP1) underlie the formation of heterochromatin and associate with transcriptional repression within the euchromatin. H3K9 methylation can occur as mono-methylation (me1), di-methylation (me2) or tri-methylation (me3). Methylation of H3K9 is catalyzed by methyltransferases (such as SUV39H, G9a), and can be removed by several lysine demethylases (KDMs). By reversing the function of H3K9 methylation, H3K9 demethylases can regulate a variety of biological processes such as gene transcription, chromatin structure and epigenetic state. The H3K9 demethylases play an important role in normal development and their aberrations are involved in diseases such as cancer. DNA

Correspondence – Jianfei Qi, Marlene and Stewart Greenebaum Comprehensive Cancer Center, Department of Biochemistry and Molecular Biology, University of Maryland, 655 W Baltimore St, Baltimore, MD, 21201 USA. jqi@som.umaryland.edu.

Author Contribution Statement

H.J. and J.Q. wrote the manuscript. A.H. edited the manuscript.

Conflicts of Interest

The authors declare no conflicts of interest.

double-strand breaks (DSBs) represent the most deleterious damage, which can cause genome instability and cell death if not properly repaired. Many epigenetic regulators, among which are H3K9 demethylases, have been shown to regulate DSB repair. Here, we will provide an overview of H3K9 demethylases, DSB repair mechanisms, and then discuss mechanisms of H3K9 demethylases in DSB repair.

H3K9 demethylases

Histone lysine demethylases (KDMs) are categorized into two families based on the catalytic mechanisms. The first family is KDM1 (also called lysine-specific demethylase, LSD), which consists of two members KDM1A (LSD1) and KDM1B (LSD2). The KDM1 family uses flavin adenine dinucleotide (FAD) as the cofactor to demethylate H3K4me1/2 in an amine oxidation reaction (1). KDM1A can also demethylate H3K9me1/2 when it binds to other proteins such as the androgen receptor (AR) (2). The second family of KDMs consists of over 24 members with demethylase activity towards H3K4, H3K9, H3K27, H3K36 or H4K20. They contain the catalytic Jumonji C (JmjC)-domain, which uses a dioxygenase mechanism to demethylate specific mono-, di- and tri-methylated lysine residues. The JmjC domain uses α -ketoglutarate, Fe (II), and molecular oxygen as cofactors in the demethylation reaction. Based on the degree of homology and the presence of other domains, the JmjC family of KDMs can be divided into 6 subfamilies (KDM2–7). Members of the KDM3, KDM4 and KDM7 subfamily exhibit H3K9 demethylase activity. KDM3 (also called JMJD1) subfamily has 3 members (KDM3A, KDM3B, KDM3C), which demethylate H3K9me1/2. KDM4 subfamily has 5 members (KDM4A, KDM4B, KDM4C, KDM4D, KDM4E). All KDM4 subfamily members can demethylate H3K9me2/3, while KDM4A–C can also demethylate H3K36me2/3 (3, 4). KDM7 subfamily has 3 members (KDM7A, KDM7B, KDM7C). KDM7B (also called PHF8) and KDM7C (also called PHF2) exhibit H3K9 demethylase activity. KDM7B (PHF8) can demethylate H3K9me1/2, H3K27me2 and H4K20me1 (5). KDM7C (PHF2) can demethylate H3K9me1/2 and H4K20me3 (6–8). In addition, H3K9 demethylases can demethylate non-histone substrates (9, 10). Some H3K9 demethylases (such as KDM3A, KDM4A–D, KDM7B) are upregulated in various cancer types, are associated with poor prognosis, and play a tumor-promoting role. Among the H3K9 demethylases, KDM3A, KDM3C, KDM4A, KDM4B, KDM4D, KDM7B and KDM7C have been reported to regulate DSB repair.

DSB repair mechanisms

DSBs can be generated by exogenous and endogenous factors such as ionizing radiation (IR), some chemotherapy agents, reactive oxygen species and replication stresses (11). DSBs activate a coordinated signaling pathway known as DNA damage response (DDR), which senses DNA damage, signals its presence and mediates its repair. Abnormality of DSB repair can cause genomic instability, cancer development or resistance of cancer to radiotherapy or genotoxic chemotherapy. DSBs are primarily repaired by two major pathways: homologous recombination (HR) and non-homologous end joining (NHEJ) (11). HR uses an undamaged DNA template on the sister chromatid or homologous chromosome to repair DSB, so it is more prevalent in the S and G2 phases of the cell cycle. By contrast, NHEJ is a process by which two broken DNA ends are ligated directly without the need for a template. DSB repair by NHEJ can occur in all stages of the cell cycle, but is favored in

the G1 phase. Unlike the precise DSB repair mediated by HR, NHEJ repair is error prone, frequently generating small insertions, deletions or substitutions at the break site.

HR initiates with binding of the MRE-11/RAD50/NBS1 (MRN) complex to the broken DNA ends, leading to activation of ATM (12). ATM induces phosphorylation of histone H2AX on Ser139 (called γ -H2AX) surrounding the DSB site (13). The binding of the mediator protein MDC1 to γ -H2AX leads to its recruitment to DSB sites (14). MDC1 itself is a substrate of ATM, and phosphorylation of MDC1 by ATM leads to recruitment of E3 ubiquitin ligase RNF8, which then recruits another E3 ubiquitin ligase RNF168 (15–17). RNF8/RNF168 cooperatively induce the formation of K63-linked polyubiquitin chains on histones surrounding the DSB site (16, 18). RNF168 also induces the mono-ubiquitination of H2A at K15 (H2AK15ub) (18). These ubiquitination events recruit RAP80/BRCA1 and 53BP1 to DSB sites (19, 20). Next, DNA end resection is initiated by endonuclease CtIP, in cooperation with MRN complex and other nucleases, to generate single strand DNA (ssDNA). The ssDNA is protected by coating with replication protein A (RPA1, RPA2, RPA3). RAD51 then replaces RPA to form a helical nucleoprotein filament on ssDNA, to initiate strand invasion on the template DNA for HR-mediated repair.

Recruitment of 53BP1 and BRCA1 to DSB sites play a key role in the DSB repair choice by NHEJ and HR, respectively. 53BP1 recruitment is mediated by H2AK15ub and H4K20me2. 53BP1 engages with H4K20me2 through its tandem Tudor domain (21) and with H2AK15ub via its UDR domain (20). 53BP1 recruits other proteins to restrict the DNA end resection, thereby inhibiting HR and promoting repair through the NHEJ pathway (22). BRCA1 can form several different complexes. The BRCA1-RAP80 (BRCA1-A complex) is recruited to the chromatin regions surrounding DSB sites through the binding of RAP80's ubiquitin-interacting motif (UIM) with K63-linked ubiquitin chains on histones (19). The BRCA1-RAP80 complex appears to restrict DNA end resection and inhibit HR DSB repair (23, 24). In direct vicinity of DSB sites, BRCA1 can form a complex with CtIP and MRN complex (BRCA1-C complex), which promotes the DNA end resection and HR repair. Recruitment of the BRCA1-C complex is independent of RNF168 (25). BRCA1 forms a heterodimer with BARD1 (26). The BRCA1-C complex is recruited to DSB sites through BARD1 interaction with HP1 associated with H3K9me2 (25). In addition, BRCA1 associates with BRCA2 through PALB2, while BRCA2 promotes the loading of RAD51 to ssDNA for efficient HR repair (27, 28). In summary, DNA end resection is a critical step differentially regulated by BRCA1 and 53BP1 that dictate the DSB repair via the HR or NHEJ pathways, respectively.

In NHEJ repair, the broken DNA ends are recognized and bound by the Ku heterodimer (Ku70 and Ku80), which blocks the DNA 5'-end resection and also serves as a scaffold to recruit other NHEJ factors (such as DNA-PK, APLF, Polymerase μ , XLF, XRCC4, DNA ligase IV, PNKP, among others). These NHEJ factors resect damaged DNA, fill in new DNA, and ligate DNA ends to restore integrity of the DNA stands (29).

Role of H3K9 demethylases in DSB repair

A. Regulate expression of DNA repair factors

JMJD1A (KDM3A)—Some DNA repair factors are known to be transcriptionally upregulated in prostate cancer. In the presence of androgen, AR can upregulate the transcription of a set of DNA repair factors (30, 31). On the other hand, the absence of androgen (castrate condition) can activate the transcription factor MYB, which replaces AR to drive the transcription of these DNA repair factors (32). We found that inhibition of JMJD1A decreased expression of another set of DNA repair factors involved with the HR (RNF8, NBS1, BARD1, SMC1A, RAD1) and NHEJ (DNA-PK, Ku70, PNKP) pathways (33). In the human prostate cancer tissue GEO dataset, JMJD1A activity correlated positively with the above JMJD1A-dependent DNA repair factors in advanced states of prostate cancer (33). We previously found that JMJD1A promotes the activities of AR and c-Myc transcription factors (34–36). However, the JMJD1A-dependent expression of DNA repair factors was primarily mediated by c-Myc and not AR (33). We found that JMJD1A can elevate c-Myc levels (34), and can also promote the chromatin recruitment of c-Myc by removing the repressive H3K9me2 marks on the promoters of DNA repair factors (33). JMJD1A knockdown in prostate cancer cells delayed the resolution of γ -H2AX foci, reduced both HR and NHEJ DSB repair activities, and enhanced the growth inhibitory effects of IR as well as topoisomerase or PARP inhibitors (33). Thus, our findings revealed a role for JMJD1A in DSB repair and radio-resistance in prostate cancer cells (Figure 1).

JMJD1A knockdown experiments revealed that JMJD1A promotes the formation of DSB foci positive for BRCA1 and RAD51 (33), key factors for HR DSB repair. We found that JMJD1A upregulates the expression of RNF8 and BARD1 (33). RNF8/RNF168-induced K63 polyubiquitination helps recruit the BRCA1-A complex to DSB sites, whereas BARD1 recruits the BRCA1-C complex to these sites. However, the relative contributions of these complex assemblies to HR DSB repair require additional studies..

JMJD1A knockdown also inhibited expression of Ku70/DNA-PK and formation of 53BP1-positive DSB foci (33). Ku70, DNA-PK and 53BP1 are key factors that govern NHEJ DSB repair. We found that JMJD1A does not affect the expression of 53BP1 (33). One of factors recruiting 53BP1 to DSB sites is H2AK15ub, which is directly induced by RNF168 in a manner strictly dependent on RNF8 (18). So JMJD1A-dependent expression of RNF8 is likely to enhance RNF168-induced H2AK15ub to recruit 53BP1 to DSB sites.

Taken together, our findings indicate that JMJD1A-dependent expression of DNA repair factors via its H3K9 demethylase activity promotes DSB repair that encompass both HR and NHEJ pathways.

PHF2 (KDM7C)—PHF2 was recently reported to promote HR DSB repair in U2OS cells (37). PHF2 knockdown decreased expression of BRCA1 and CtIP, key factors the promote DNA end resection necessary for HR DSB repair (37). Consistently, PHF2 knockdown reduced the accumulation of RPA2 and RAD51 at DSB sites, and decreased CtIP-mediated DNA end resection (37). The histone demethylase activity of PHF2 was required for the expression of BRCA1 and CtIP (37). As PHF2 can demethylate both H3K9me1/2 and

H4K20me3, it remains to determine which of these demethylating activities of PHF2 is required.

Another study in neural progenitor cells reported the role of PHF2 in regulating the expression of genes involved in HR DSB repair (ATM, BRCA1, RAD51), DNA replication and cell cycle (38). PHF2 promotes the expression of these genes likely via H3K9 demethylation on the respective gene promoters. Accordingly, knockdown of PHF2 in neural progenitor cells induced R-loop accumulation that led to DSB damage (38). Thus, PHF2 can prevent DSB damage in neural progenitor cells by regulating gene expression through its H3K9 demethylase activity.

B. Function at DSB sites

JMJD1C (KDM3C)—In contrast to JMJD1A, JMJD1C has been implicated in inhibiting HR DSB repair in U2OS cells (9). JMJD1C interaction with RNF8/RNF168 appears to be necessary for its recruitment to DSB sites (9). Knockdown of JMJD1C inhibits the recruitment of RNF8, RAP80 and BRCA1 to DSB sites (9). JMJD1C knockdown, on the other hand, has no effect on 53BP1 foci formation. Thus, JMJD1C-RNF8 interactions selectively enhance the recruitment of RAP80-BRCA1 (BRCA1-A complex) to DSB foci. Mechanistically, JMJD1C has no effect on H3K9me2 levels at DSB sites, and rather demethylates MDC1 to enhance the interaction of RNF8 with MDC1 after radiation treatment. Knockdown of JMJD1C increases the formation of RAD51 foci and enhances the resistance of cells to radiation or PARP inhibitors (9). Together, these results suggest that JMJD1C activity inhibits HR DSB repair by enhancing the recruitment of RAP80-BRCA1 to DSB sites. Although JMJD1A and JMJD1C belong to the KDM3 subfamily and both can demethylate H3K9, they appear to use different mechanisms and have different effect on DSB repair. JMJD1A upregulates expression of DSB repair factors and promotes the DSB repair via both HR and NHEJ pathways, whereas JMJD1C is recruited to DSB sites and inhibits HR DSB repair. Thus, JMJD1A and JMJD1C mediate opposite effects in terms of cell response to radiation or PARP inhibitors.

KDM4A and KDM4B—One study implicates that KDM4A and KDM4B may inhibit DSB repair in U2OS cells (39). KDM4A and KDM4B were found to undergo the ubiquitination-mediated degradation by RNF8 and RNF168 upon DSB damages (39). Ectopic overexpression of KDM4A or KDM4B inhibited the accumulation of 53BP1 at DSB foci. Further, the tandem Tudor domain of KDM4A, but not its histone demethylase activity, was found to inhibit 53BP1 recruitment to DSB sites (39). This domain is present in KDM4A, KDM4B and 53BP1. One mechanism by which 53BP1 gets recruited to DSB sites is via the interaction of its tandem Tudor domain with H4K20me2 marks on chromatin (21). As the tandem Tudor domain of KDM4A or KDM4B has higher affinity for H4K20me2 than that of 53BP1 (39), KDM4A or KDM4B may competitively inhibit the recruitment of 53BP1 to H4K20me2 at DSB sites. Ubiquitination-mediated degradation of KDM4A and KDM4B by RNF8/RNF168 remove these demethylases from H4K20me2, thus allowing binding of 53BP1 to occur at the DSB sites. Ectopic overexpression of KDM4A was found to sensitize U2OS cells to etoposide treatment (39), suggesting that KDM4A- or KDM4B-mediated DNA repair inhibition can sensitize cancer cells to DNA damaging agents. To what extent

KDM4A or KDM4B modulates the HR and/or NHEJ DSB repair pathways, however, needs to be further elucidated.

In contrast, two other studies implicate KDM4B in promoting rather than inhibiting DSB repair in U2OS cells (40, 41). One study showed that GFP-tagged KDM4B was recruited to DSB sites, reduced H3K9me2 level, promoted resolution of γ -H2AX foci and enhanced survival of U2OS cells after radiation (40). Another study showed that KDM4B was transcriptionally upregulated by p53 upon treatment of U2OS cells with radiation (41). Further, knockdown of KDM4B in U2OS cells delayed the resolution of γ -H2AX foci on heterochromatin, and sensitized the cells to radiation and chemotherapeutic drugs (41). Some of the experimental conditions may have contributed to the disparate reports on KDM4B's role in DSB repair and worth additional work for further clarification.

KDM4D—KDM4D has been reported to promote DSB repair in U2OS and A172 cells (42, 43). Recruitment of KDM4B to DSB sites is dependent on the PARP1-induced ADP-ribosylation (42, 43). KDM4D was found to increase recruitment of ATM to chromatin upon DSB damage (42). Consistent with this, knockdown of KDM4D in U2OS cells reduced the formation of DSB foci positive for γ -H2AX, 53BP1 and RAD51, inhibited HR DSB repair, and sensitized cells to radiation (42). The H3K9 demethylase function of KDM4D was required for HR DSB repair activity (42). It remains to determine whether the H3K9 demethylase activity of KDM4D regulates chromatin recruitment of ATM and if so what is the underlying mechanism for such processes.

PHF8 (KDM7B)—PHF8 has been reported to promote DSB repair in MCF-7 cells (44). PHF8 was recruited to DSB sites in MCF-7 cells. Knockdown of PHF8 reduced both HR and NHEJ DSB repair in a manner dependent on its demethylase activity (44). PHF8 was found to interact with BLM, a regulator of DNA end resection in HR DSB repair, suggesting that PHF8 may facilitate recruitment of BLM to DSB site for efficient DNA end resection during HR DSB repair. In addition, knockdown of PHF8 inhibited the recruitment of Ku70 that promotes NHEJ DSB repair. Thus, this study suggests that PHF8 may promote HR and NHEJ DSB repair by facilitating the recruitment of BLM and Ku70, respectively, to DSB sites (44). Of note, knockdown of PHF8 had no effect on the levels of H3K9me1/2, H3K27me2 and H4K20me1 at the DSB sites, and so it remains to determine how the demethylating activity of PHF8 promotes DSB repair.

The function of PHF8 in DSB repair is conserved in *C.elegans*, which has a PHF8 homolog named JMJD-1.1. Epistatic analysis of the Jmjd-1.1 mutant worm has shown that JMJD-1.1 functions in the HR DSB repair pathway (45). In the Jmjd-1.1 mutant worm treated with radiation, the formation of RPA1 and RAD51 foci in mitotic germ cells was normal, but their dissociation was delayed (45), suggesting that JMJD-1.1 in *C.elegans* promotes HR DSB repair at a step further downstream of RPA1/RAD51 loading onto ssDNA.

Discussion and Conclusion

In summary, some H3K9 demethylases (JMJD1A, PHF2) use their demethylase activity to regulate the expression of DSB repair factors, and thus indirectly modulate DSB repair.

Other H3K9 demethylases (JMJD1C, KDM4D, PHF8) are recruited to DSB sites, and directly regulate the recruitment or function of DSB repair factors.

The catalytic activity of some of H3K9 demethylases (KDM4D, PHF8) is required for DSB repair, but the underlying mechanisms remain unclear. Although it is tempting to speculate that H3K9 demethylases by removing H3K9 methylation marks at DSB sites may relax chromatin to allow recruitment and access of DSB repair factors, in the vast majority of published studies no apparent changes in H3K9 methylation marks are observed upon treatment of cells with DNA damaging agents. Only a handful of studies have reported alterations in H3K9 methylation marks. One study showed transient reductions in the total levels of H3K9me_{2/3} after treatment of U2OS cells with radiation (40), while another study showed transient reductions in the levels of heterochromatin-associated H3K9me₃ after treatment of HCT116 cells with radiation (41). Conversely, other studies have suggested that increase in H3K9 methylation can occur at DSB sites (46, 47). For instance, one study showed increased levels of H3K9me₃ surrounding nuclease-induced DSB sites within the PPP1R12C gene of 293T cells (46), while another study showed increased levels of H3K9me₂ surrounding nuclease-induced DSB sites within a puromycin acetyltransferase gene of the engineered HT1904 cell model (47). Further, another study showed that the levels of H3K9me₂ were reduced within 20 minutes, restored to normal levels at 40 minutes, and then gradually increased thereafter up to 120 minutes after treatment of human fibroblasts with radiation (48). These studies suggest that H3K9 methylation and demethylation may be a dynamic and transient process regulated by methyltransferases and demethylases during the DSB repair. Thus, alterations of H3K9 methylation at DSB sites may be difficult to detect by some of the current approaches, and will require further study. Alternatively, H3K9 demethylases may demethylate other histone marks or non-histone proteins during DSB repair. For example, KDM1A (LSD1) has been shown to regulate DSB repair by demethylating H3K4me₂, but not H3K9me₂ (49). JMJD1C is shown to regulate DSB repair by demethylating MDC1 and not H3K9me₂ (9).

H3K9 demethylases such as JMJD1A, KDM4D, PHF2 and PHF8 can promote DSB repair dependent on their catalytic activity. Many inhibitors of H3K9 demethylases are in active development as potential therapeutic agents (50). It will be interesting to determine whether the inhibitors of H3K9 demethylases can be used to enhance the response of cancer cells to radiotherapy or genotoxic chemotherapy.

Funding

This study is supported by NCI grant R01CA207118 and a V Scholar award (to J.Q.). Part of A.H.'s time was supported by a Merit Review Award (I01 BX000545), Medical Research Service, Department of Veterans Affairs.

Abbreviations

AR	Androgen Receptor
DDR	DNA damage response
DSBs	Double-Strand Breaks

H3K9	Histone H3 Lysine-9
HP1	Heterochromatin Protein 1
HR	Homologous Recombination
IR	Ionizing Radiation
JmjC	Jumonji C
KDMs	Lysine Demethylases
MRN	MRE-11/RAD50/NBS1
NHEJ	Non-Homologous End Joining
RPA	Replication Protein A
ssDNA	single strand DNA

References

1. Shi Y, Lan F, Matson C, Mulligan P, Whetstone JR, Cole PA, et al. Histone demethylation mediated by the nuclear amine oxidase homolog LSD1. *Cell*. 2004;119(7):941–53. [PubMed: 15620353]
2. Metzger E, Wissmann M, Yin N, Muller JM, Schneider R, Peters AH, et al. LSD1 demethylates repressive histone marks to promote androgen-receptor-dependent transcription. *Nature*. 2005;437(7057):436–9. [PubMed: 16079795]
3. Cloos PA, Christensen J, Agger K, Maiolica A, Rappsilber J, Antal T, et al. The putative oncogene GASC1 demethylates tri- and dimethylated lysine 9 on histone H3. *Nature*. 2006;442(7100):307–11. [PubMed: 16732293]
4. Whetstone JR, Nottke A, Lan F, Huarte M, Smolikov S, Chen Z, et al. Reversal of histone lysine trimethylation by the JMJD2 family of histone demethylases. *Cell*. 2006;125(3):467–81. [PubMed: 16603238]
5. Qi HH, Sarkissian M, Hu GQ, Wang Z, Bhattacharjee A, Gordon DB, et al. Histone H4K20/H3K9 demethylase PHF8 regulates zebrafish brain and craniofacial development. *Nature*. 2010;466(7305):503–7. [PubMed: 20622853]
6. Wen H, Li J, Song T, Lu M, Kan PY, Lee MG, et al. Recognition of histone H3K4 trimethylation by the plant homeodomain of PHF2 modulates histone demethylation. *J Biol Chem*. 2010;285(13):9322–6. [PubMed: 20129925]
7. Bricambert J, Alves-Guerra MC, Esteves P, Prip-Buus C, Bertrand-Michel J, Guillou H, et al. The histone demethylase Phf2 acts as a molecular checkpoint to prevent NAFLD progression during obesity. *Nat Commun*. 2018;9(1):2092. [PubMed: 29844386]
8. Stender JD, Pascual G, Liu W, Kaikkonen MU, Do K, Spann NJ, et al. Control of proinflammatory gene programs by regulated trimethylation and demethylation of histone H4K20. *Mol Cell*. 2012;48(1):28–38. [PubMed: 22921934]
9. Watanabe S, Watanabe K, Akimov V, Bartkova J, Blagoev B, Lukas J, et al. JMJD1C demethylates MDC1 to regulate the RNF8 and BRCA1-mediated chromatin response to DNA breaks. *Nat Struct Mol Biol*. 2013;20(12):1425–33. [PubMed: 24240613]
10. Ramadoss S, Guo G, Wang CY. Lysine demethylase KDM3A regulates breast cancer cell invasion and apoptosis by targeting histone and the non-histone protein p53. *Oncogene*. 2017;36(1):47–59. [PubMed: 27270439]
11. Ciccio A, Elledge SJ. The DNA damage response: making it safe to play with knives. *Mol Cell*. 2010;40(2):179–204. [PubMed: 20965415]
12. Lavin MF. ATM and the Mre11 complex combine to recognize and signal DNA double-strand breaks. *Oncogene*. 2007;26(56):7749–58. [PubMed: 18066087]

13. Burma S, Chen BP, Murphy M, Kurimasa A, Chen DJ. ATM phosphorylates histone H2AX in response to DNA double-strand breaks. *J Biol Chem*. 2001;276(45):42462–7. [PubMed: 11571274]
14. Stucki M, Clapperton JA, Mohammad D, Yaffe MB, Smerdon SJ, Jackson SP. MDC1 directly binds phosphorylated histone H2AX to regulate cellular responses to DNA double-strand breaks. *Cell*. 2005;123(7):1213–26. [PubMed: 16377563]
15. Kolas NK, Chapman JR, Nakada S, Ylanko J, Chahwan R, Sweeney FD, et al. Orchestration of the DNA-damage response by the RNF8 ubiquitin ligase. *Science*. 2007;318(5856):1637–40. [PubMed: 18006705]
16. Doil C, Mailand N, Bekker-Jensen S, Menard P, Larsen DH, Pepperkok R, et al. RNF168 binds and amplifies ubiquitin conjugates on damaged chromosomes to allow accumulation of repair proteins. *Cell*. 2009;136(3):435–46. [PubMed: 19203579]
17. Thorslund T, Ripplinger A, Hoffmann S, Wild T, Uckelmann M, Villumsen B, et al. Histone H1 couples initiation and amplification of ubiquitin signalling after DNA damage. *Nature*. 2015;527(7578):389–93. [PubMed: 26503038]
18. Mattioli F, Vissers JH, van Dijk WJ, Ikpa P, Citterio E, Vermeulen W, et al. RNF168 ubiquitinates K13–15 on H2A/H2AX to drive DNA damage signaling. *Cell*. 2012;150(6):1182–95. [PubMed: 22980979]
19. Sobhian B, Shao G, Lilli DR, Culhane AC, Moreau LA, Xia B, et al. RAP80 targets BRCA1 to specific ubiquitin structures at DNA damage sites. *Science*. 2007;316(5828):1198–202. [PubMed: 17525341]
20. Fradet-Turcotte A, Canny MD, Escibano-Diaz C, Orthwein A, Leung CC, Huang H, et al. 53BP1 is a reader of the DNA-damage-induced H2A Lys 15 ubiquitin mark. *Nature*. 2013;499(7456):50–4. [PubMed: 23760478]
21. Botuyan MV, Lee J, Ward IM, Kim JE, Thompson JR, Chen J, et al. Structural basis for the methylation state-specific recognition of histone H4-K20 by 53BP1 and Crb2 in DNA repair. *Cell*. 2006;127(7):1361–73. [PubMed: 17190600]
22. Panier S, Boulton SJ. Double-strand break repair: 53BP1 comes into focus. *Nat Rev Mol Cell Biol*. 2014;15(1):7–18. [PubMed: 24326623]
23. Coleman KA, Greenberg RA. The BRCA1-RAP80 complex regulates DNA repair mechanism utilization by restricting end resection. *J Biol Chem*. 2011;286(15):13669–80. [PubMed: 21335604]
24. Hu Y, Scully R, Sobhian B, Xie A, Shestakova E, Livingston DM. RAP80-directed tuning of BRCA1 homologous recombination function at ionizing radiation-induced nuclear foci. *Genes Dev*. 2011;25(7):685–700. [PubMed: 21406551]
25. Wu W, Nishikawa H, Fukuda T, Vittal V, Asano M, Miyoshi Y, et al. Interaction of BARD1 and HP1 Is Required for BRCA1 Retention at Sites of DNA Damage. *Cancer Res*. 2015;75(7):1311–21. [PubMed: 25634209]
26. Wu LC, Wang ZW, Tsan JT, Spillman MA, Phung A, Xu XL, et al. Identification of a RING protein that can interact in vivo with the BRCA1 gene product. *Nat Genet*. 1996;14(4):430–40. [PubMed: 8944023]
27. Sy SM, Huen MS, Chen J. PALB2 is an integral component of the BRCA complex required for homologous recombination repair. *Proc Natl Acad Sci U S A*. 2009;106(17):7155–60. [PubMed: 19369211]
28. Roy R, Chun J, Powell SN. BRCA1 and BRCA2: different roles in a common pathway of genome protection. *Nat Rev Cancer*. 2011;12(1):68–78. [PubMed: 22193408]
29. Davis AJ, Chen DJ. DNA double strand break repair via non-homologous end-joining. *Transl Cancer Res*. 2013;2(3):130–43. [PubMed: 24000320]
30. Goodwin JF, Schiewer MJ, Dean JL, Schrecengost RS, de Leeuw R, Han S, et al. A hormone-DNA repair circuit governs the response to genotoxic insult. *Cancer Discov*. 2013;3(11):1254–71. [PubMed: 24027197]
31. Polkinghorn WR, Parker JS, Lee MX, Kass EM, Spratt DE, Iaquinta PJ, et al. Androgen receptor signaling regulates DNA repair in prostate cancers. *Cancer Discov*. 2013;3(11):1245–53. [PubMed: 24027196]

32. Li L, Chang W, Yang G, Ren C, Park S, Karantanos T, et al. Targeting poly(ADP-ribose) polymerase and the c-Myb-regulated DNA damage response pathway in castration-resistant prostate cancer. *Sci Signal*. 2014;7(326):ra47. [PubMed: 24847116]
33. Fan L, Xu S, Zhang F, Cui X, Fazli L, Gleave M, et al. Histone demethylase JMJD1A promotes expression of DNA repair factors and radio-resistance of prostate cancer cells. *Cell Death Dis*. 2020;11(4):214. [PubMed: 32238799]
34. Fan L, Peng G, Sahgal N, Fazli L, Gleave M, Zhang Y, et al. Regulation of c-Myc expression by the histone demethylase JMJD1A is essential for prostate cancer cell growth and survival. *Oncogene*. 2016;35(19):2441–52. [PubMed: 26279298]
35. Fan L, Zhang F, Xu S, Cui X, Hussain A, Fazli L, et al. Histone demethylase JMJD1A promotes alternative splicing of AR variant 7 (AR-V7) in prostate cancer cells. *Proc Natl Acad Sci U S A*. 2018;115(20):E4584–E93. [PubMed: 29712835]
36. Wilson S, Fan L, Sahgal N, Qi J, Filipp FV. The histone demethylase KDM3A regulates the transcriptional program of the androgen receptor in prostate cancer cells. *Oncotarget*. 2017;8(18):30328–43. [PubMed: 28416760]
37. Alonso-de Vega I, Paz-Cabrera MC, Rother MB, Wiegant WW, Checa-Rodriguez C, Hernandez-Fernaund JR, et al. PHF2 regulates homology-directed DNA repair by controlling the resection of DNA double strand breaks. *Nucleic Acids Res*. 2020.
38. Pappa S, Padilla N, Iacobucci S, Vicioso M, Alvarez de la Campa E, Navarro C, et al. PHF2 histone demethylase prevents DNA damage and genome instability by controlling cell cycle progression of neural progenitors. *Proc Natl Acad Sci U S A*. 2019;116(39):19464–73. [PubMed: 31488723]
39. Mallette FA, Mattioli F, Cui G, Young LC, Hendzel MJ, Mer G, et al. RNF8- and RNF168-dependent degradation of KDM4A/JMJD2A triggers 53BP1 recruitment to DNA damage sites. *EMBO J*. 2012;31(8):1865–78. [PubMed: 22373579]
40. Young LC, McDonald DW, Hendzel MJ. Kdm4b histone demethylase is a DNA damage response protein and confers a survival advantage following gamma-irradiation. *J Biol Chem*. 2013;288(29):21376–88. [PubMed: 23744078]
41. Zheng H, Chen L, Pledger WJ, Fang J, Chen J. p53 promotes repair of heterochromatin DNA by regulating JMJD2b and SUV39H1 expression. *Oncogene*. 2014;33(6):734–44. [PubMed: 23376847]
42. Khoury-Haddad H, Guttmann-Raviv N, Ipenberg I, Huggins D, Jeyasekharan AD, Ayoub N. PARP1-dependent recruitment of KDM4D histone demethylase to DNA damage sites promotes double-strand break repair. *Proc Natl Acad Sci U S A*. 2014;111(7):E728–37. [PubMed: 24550317]
43. Khoury-Haddad H, Nadar-Ponniah PT, Awwad S, Ayoub N. The emerging role of lysine demethylases in DNA damage response: dissecting the recruitment mode of KDM4D/JMJD2D to DNA damage sites. *Cell Cycle*. 2015;14(7):950–8. [PubMed: 25714495]
44. Wang Q, Ma S, Song N, Li X, Liu L, Yang S, et al. Stabilization of histone demethylase PHF8 by USP7 promotes breast carcinogenesis. *J Clin Invest*. 2016;126(6):2205–20. [PubMed: 27183383]
45. Lee C, Hong S, Lee MH, Koo HS. A PHF8 homolog in *C. elegans* promotes DNA repair via homologous recombination. *PLoS One*. 2015;10(4):e0123865. [PubMed: 25853498]
46. Ayrappetov MK, Gursoy-Yuzugullu O, Xu C, Xu Y, Price BD. 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*. 2014;111(25):9169–74. [PubMed: 24927542]
47. Fnu S, Williamson EA, De Haro LP, Brennenman M, Wray J, Shaheen M, et al. Methylation of histone H3 lysine 36 enhances DNA repair by nonhomologous end-joining. *Proc Natl Acad Sci U S A*. 2011;108(2):540–5. [PubMed: 21187428]
48. Falk M, Lukasova E, Gabrielova B, Ondrej V, Kozubek S. Chromatin dynamics during DSB repair. *Biochim Biophys Acta*. 2007;1773(10):1534–45. [PubMed: 17850903]
49. Mosammaparast N, Kim H, Laurent B, Zhao Y, Lim HJ, Majid MC, et al. The histone demethylase LSD1/KDM1A promotes the DNA damage response. *J Cell Biol*. 2013;203(3):457–70. [PubMed: 24217620]

50. McAllister TE, England KS, Hopkinson RJ, Brennan PE, Kawamura A, Schofield CJ. Recent Progress in Histone Demethylase Inhibitors. *J Med Chem.* 2016;59(4):1308–29. [PubMed: 26710088]

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Figure 1.

JMJD1A activity in prostate cancer cells increases the level of c-Myc and also enhances the c-Myc chromatin recruitment by demethylating H3K9me2 marks on the gene promoters of indicated DNA repair factors for HR or NHEJ. JMJD1A may also regulate the activity of another unidentified transcription factor to upregulate the expression of RNF8. The elevated expression of these DNA repair factors leads to the enhanced DSB repair by both HR and NHEJ pathways. Thus, JMJD1A activity contributes to the resistance of prostate cancer cells to IR, topoisomerase inhibitors or PARP inhibitors.