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Review

Histone methylation can either promote or reduce cellular radiosensitivity by regulating DNA repair pathways

Yuchuan Zhou, Chunlin Shao*

Institute of Radiation Medicine, Shanghai Medical College, Fudan University, No. 2094 Xie-Tu Road, Shanghai, 200032, China

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ABSTRACT

Radiotherapy is one of the primary modalities for cancer treatment, and its efficiency usually relies on cellular radiosensitivity. DNA damage repair is a core content of cellular radiosensitivity, and the primary mechanism of which includes non-homologous end-joining (NHEJ) and homologous recombination (HR). By affecting DNA damage repair, histone methylation regulated by histone methyltransferases (HMTs) and histone demethylases (HDMs) participates in the regulation of cellular radiosensitivity via three mechanisms: (a) recruiting DNA repair-related proteins, (b) regulating the expressions of DNA repair genes, and (c) mediating the dynamic change of chromatin. Interestingly, both aberrantly high and low levels of histone methylation could impede DNA repair processes. Here we reviewed the mechanisms of the dual effects of histone methylation on cell response to radiation. Since some inhibitors of HMTs and HDMs are reported to increase cellular radiosensitivity, understanding their molecular mechanisms may be helpful in developing new drugs for the therapy of radioresistant tumors.

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* Corresponding author.
E-mail address: clshao@shmu.edu.cn (C. Shao).

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1. Introduction

Radiotherapy is one of the primary modalities of cancer treatment and about 50 % of cancer patients benefit from radiotherapy [1]. The cellular radiosensitivity of tumor is a pivotal point to the preferable efficacy of radiotherapy, which can be regulated by many factors, including DNA damage repair ability, cell cycle progression, and intrinsic autophagy level [2,3]. It is well-known that the initial event of radiation response is DNA damage [4], including single-strand breaks (SSBs), double-strand breaks (DSBs), base damages, cross-linking and others [5]. The incidence of DNA damage, especially DSBs, could trigger sophisticated DNA repair pathways [6].

Histone methylation is a process by which methyl groups are transferred to amino acids of histone proteins at basic residues of arginine, lysine, and histidine [7]. Histone methyltransferases (HMTs) and histone demethylases (HDMs) are required in this process. All of the above amino acids can be monomethylated (me1), while the arginine and lysine can be dimethylated (me2), but only the lysine can be trimethylated (me3) [7]. Histone methylation can influence DNA damage repair, cell apoptosis, cell cycle progression, autophagy, and other biological processes closely related to cellular radiosensitivity [8–10]. Common methylation sites associated with DNA damage repair include histone H3 lysine 4 (H3K4), H3K9, H3K27, H3K36, H3K79 and H4K20. Generally, the methylation of H3K4, H3K36 and H3K79 is essential for gene-activating event, while the methylation of H3K9, H3K27 and H4K20 stands for gene-repressing event [11]. In recent years, some studies have identified that histone methylation has specific expression profiles in radioresistant and radiosensitive tissues and is a potential independent prognostic molecular marker. Interestingly, there is plenty of evidence demonstrates that even the same type of histone methylation can either promote or reduce cellular radiosensitivity by differentially affecting DNA repair. In this review, the effects and regulatory mechanisms of histone methylation on cellular radiosensitivity are summarized.

2. The effect of histone methylation on cellular radiosensitivity

2.1. DNA damage response after irradiation

DNA repair is considered as the heart of cell response to radiation. There are two main pathways for DSB repair i.e., homologous recombination (HR) and nonhomologous end-joining (NHEJ). Moreover, the dynamic changes of chromatin also have a significant effect on the process of DSB repair. In general, histone methylation can regulates these DSB repair pathways and then affects cellular radiosensitivity.

2.1.1. HR repair

HR is considered as an error-free repair mechanism of DSB, during which the homologous sequence on the sister chromatid is precisely filled in the DSB gaps in order to restore the original DNA sequence [12,13]. In the first step of HR, the DSB ends are identified by a complex (named MRN) composed of meiotic recombination 11 homolog A (MRE11), RAD50 and Nijmegen breakage syndrome 1 (NBS1). This MRN complex takes the responsibility of the activation of ataxia telangiectasia mutated (ATM) that can phosphorylate several substrates to facilitate the recognition of DSB and the activation of downstream DNA repair-related proteins [14]. MRE11 is associated with nucleases such as CtIP, EXO1 and DNA2, which allows for the resection of ssDNA ends [15–18]. Meanwhile, BRCA1 is involved in the phosphorylation of CtIP by cooperating with the MRN complex [19]. Then the heterotrimeric replication protein A (RPA) quickly binds to single-strand tails, preventing ssDNA from degrading or forming a secondary structure [20]. After that, RAD51 displaces RPA to facilitate strand invasion into the sister chromatid to form the Holliday junction [21,22]. Next, the crossover junctions are resolved by resolvases to complete the DSB repair process [22]. Since RAD51 can promote the initiation of DNA synthesis at DSB region, it has been considered as the central protein of HR [23].

2.1.2. NHEJ repair

Since the probability of short insertions/deletions of genomic DNA, NHEJ is considered an error-prone repair mechanism. In the first step of NHEJ, DSB ends are recognized and encircled by the heterodimeric protein Ku70/Ku80 that further recruits DNA protein kinase catalytic subunit (DNA-PKcs) to activate a series of downstream repair processes [24,25]. In the second phase, DSB ends are removed by different nucleases, such as Artemis [26], to provide nucleolytic process before ligation [27]. Finally, DNA ligase IV is bound to a scaffold protein termed X-ray cross-complementing protein (XRCC4) to form XRCC4-DNA ligase IV complex that is recruited by Ku proteins to ligate DSB ends [24,26,28]. During the process of NHEJ, 53BP1 is vital in protecting broken DNA ends from extensive resection in the XRCC4-dependent pathway [29,30]. Accordingly, 53BP1 has been considered as the central protein of NHEJ.

2.1.3. Dynamic changes of chromatin in DNA damage sites

The complex organization of chromatin occurs during DSB repair, and evidence shows that the compacted chromatin structure represents an essential obstacle to the efficient detection and repair of DSBs [31]. Previous studies have demonstrated that DNA damage leads to a decrease of chromatin compaction during DNA repair [32]. In other words, an open chromatin structure can be induced at DNA damage sites and it allows DNA repair machinery to get access the damaged DNA sites and to perform repair functions [33–35].

However, recent work has suggested that a transient (seconds to minutes) compaction of chromatin may precede the shift to an open chromatin structure at DSB sites [36]. The transient accumulation of compacted chromatin structure at DSBs has a notable effect on preventing the passage of RNA polymerases through damaged regions and repressing local transcription [37–40]. Besides, the compacted chromatin structure may temporarily reduce the mobility of nucleosome and damaged chromatin and thus limit the ends of the broken DNA strands to have a short distance during the initial stages of DNA repair [8]. Keeping the spatial structure of broken DSBs' ends in a short distance is of great significance for the proper repair of damaged DNA. Thus, a growing body of studies have recognized the importance of chromatin remodeling in cell response to radiation. In our opinion, the impaired chromatin remodeling may inhibit DNA repair process and thus increase cellular radiosensitivity.

2.2. Role of histone methylation in recruiting DNA repair-related proteins

2.2.1. H3K4

After DNA damage occurrence, histone methyltransferase and demethylase are recruited to DSB sites to change the levels of histone methylation. Some reports have shown that the processes of NHEJ and HR repair lead to the demethylation of H3K4. KDM5B, a member of histone demethylases, can recruit Ku70 and BRCA1 to promote NHEJ and HR repair [41]. Besides, KDM5B can catalyze the demethylation of H3K4 [42] but it can be inhibited by Jumonji inhibitor JIB-04 [43]. The inhibition of KDM5B by JIB-04 results in the high level of H3K4me3 and thus impairs the recruitment of DNA repair-related proteins and reduces the efficacies of HR and NHEJ repair, in consequence, sensitizes lung cancer cells to radiation [43]. Other studies demonstrate that some small molecule inhibitors of KDM5 histone demethylases can increase the accumulation of γH2AX after radiation and thus increases the radiosensitivity of breast cancer cells [44]. KDM5A is another histone demethylase of H3K4, and the depletion of KDM5A results in a high level of intracellular H3K4me3 and sensitizes cells to ionizing radiation significantly [45].

H3K4me2 is also involved in the regulation of cellular radiosensitivity. According to the study of Peng et al. (2015) [46], lysine-specific demethylase 1A (LSD1) can be recruited to DNA damage sites and then regulates the demethylation of H3K4me2 to activate DNA repair process. Thus, knockdown of LSD1 results in high-level H3K4me2 that lead to G2/M arrest and impaired 53BP1 and BRCA1 complex recruitment, which increases cellular radiosensitivity and genomic instability [47,48].

2.2.2. H3K27

The di- and tri-methylation of H3K27 are mediated by EZH1 and EZH2, two catalytic subunits of polycomb repressive complex 2 (PRC2) [49]. When DNA damage occurs, EZH2 is recruited to DSB sites by PARP to facilitate the trimethylation of H3K27 and repress gene transcription [50]. After approaching to DNA damage sites, EZH2 further recruits MUS81 nuclease through H3K27me3 to stabilize the stalled replication forks, which is beneficial to HR repair [51,52]. Simultaneously, reduction in H3K27me2/3 caused by a mutation of H3 variant dramatically reduces the presence of 53BP1 foci at DSB sites and then decreases the capability of NHEJ in human dermal fibroblasts [53]. Inhibition of EZH2 can significantly promote genotoxicity and cytotoxicity of DNA damaging agents [54]. Some studies support that the methylation of H3K27 through EZH2 is correlated with radioresistance. Inhibition of EZH2 by RNAi or chemical inhibitor suppresses cell growth, leads to cell cycle alteration, increases γH2AX foci and apoptosis, and potentiates radiation damage in tumor cells [55–60].

2.2.3. H3K36

H3K36 methylation can be involved in cell response to radiation by regulating the processes of HR and NHEJ repair. In general, H3K36 methylation provides a site for the recruitment and activation of DNA repair-related proteins. For example, H3K36me3 can recruit RAD51 to improve HR repair. Unlike other types of histone methylation, H3K36me3 is pre-existed before DNA damage [40] and masked by lens epithelium-derived growth factor (LEDGF) [61]. The recruitment of RAD51 depends on the H3K36me3-LEDGF axis. After irradiation, LEDGF recruits CtIP to DSB sites for the enrichment of RAD51 [61]. SETD2 is the main tri-methyltransferase on H3K36 and H3K36me3 can promote DSB resection by facilitating the recruitment of CtIP [62,63]. Meanwhile, SETD2-dependent H3K36 trimethylation is necessary for the activation of ATM and the formation of 53BP1 at DSB sites [64]. Consistently, depletion of SETD2 leads to the decrease of p53 activation, impairs recruitment of RPA and RAD51, and blocks HR repair [40,62,64]. A recent study indicates that H3K36me3-enriched DSBs prefer to have HR repair, while those regions with inactive transcription and low level of H3K36me3 tend to perform NHEJ repair [40].

Unlike H3K36me3 often being involved in HR repair, di-methylated H3K36 mainly functions in NHEJ repair [65]. Activated by ATM, checkpoint kinase 1 (Chk1) can enhance DNA repair by phosphorylating downstream effectors including Metnase [66]. Metnase, a methyltransferase of H3K36, can promote NHEJ repair and increase cellular resistance to ionizing radiation [67]. Metnase takes responsibility for the rapid formation of H3K36me2 to mediate NHEJ repair after irradiation [67]. H3K36me2 can recruit NHEJ effector proteins of Ku70, PHRF1 (PHD and ring finger domain 1) and NBS1 [65]. Moreover, H3K36 dimethylation makes it easier for PHRF1 and NBS1 to bind to DSB sites and stabilizes genomic integrity upon DSBs [68,69].

Considering the function of H3K36 methylation in promoting HR and NHEJ repair, there are many reports that low-level H3K36 methylation may block the recruitment of DNA repair-related proteins to increase cellular radiosensitivity. For instance, JMJD2 (Jumonji C domain-containing 2) is a family of histone demethylases and can remove the tri-methyl group from H3K36 [70]. Overexpression of JMJD2A results in the decrease of H3K36 methylation and reduces HR repair [62]. Upregulation of JMJD2 leads to low-level H3K36 methylation and incomplete DNA damage repair, which eventually causes genetic instability and tumorigenesis. Simultaneously, inhibition of JMJD2 is associated with a good prognosis of lung cancers by down-regulating ATR and Chk1 [71]. Since H3K36 methylation is necessary for the initiation of DNA repair, an excessively low level of H3K36 methylation impairs the initiation of DNA repair, thus leading to the increase of cellular radiosensitivity.

However, in the late stages of DSB repair, the H3K36 methylation level is decreased to prevent the formation of stalled postsynaptic recombination intermediates and facilitate the removal of RAD51 [72]. We suspect that in the early stages of DNA repair, the methylation of H3K36 is conducive to recruiting DNA repair-related proteins. Nevertheless, H3K36 needs to be demethylated to facilitate the next step of DNA repair. Therefore, the inhibition of histone demethylase of H3K36 may block the DNA repair process and increase cellular radiosensitivity. A study showed that inhibition of histone demethylase JMJD2B could activate apoptotic signaling pathways after radiation [73]. Loss of histone demethylase JMJD5 leads to high-levels of H3K36me2 and aberrant retention of RAD51 at DSB sites and thus results in meiotic defects and hypersensitivity to ionizing radiation [72]. Simultaneously, down-regulation of JMJD5 suppresses metastasis and induces apoptosis in cancer [74]. These studies suggest that the aberrantly high level of H3K36 methylation may also block the DNA damage repair process and thus increases cellular radiosensitivity.

2.2.4. H3K79

H3K79 methylation is strongly correlated with 53BP1. Disruptor of telomeric silencing-1 (Dot1/DOT1L) is an evolutionarily conserved histone methyltransferase of lysine 79 [75]. The current research on the mechanism of H3K79 methylation affecting DNA damage repair is mainly based on yeast. For instance, loss of Dot1 prevents activation of Rad9 (the yeast 53BP1 ortholog) and decreases the recruitment of Rad9 to DSBs after DNA damage in yeast [76]. H3K79 methylation can recruit 53BP1 to drive NHEJ repair in the G1/G2 phase [77,78], whereas mutation of H3K79 or depletion of DOT1L causes the inhibition of H3K79 methylation and impairs the recruitment of 53BP1 to DSBs [75]. Leading to Dot1-dependent dimethylation of H3K79 (H3K79me2) [79], Bre1

is essential for the recruitment of checkpoint protein Rad9 to DSB sites in Saccharomyces cerevisiae [80]. Knocking-down Bre1 allows cells to be more vulnerable to radiation [81].

Low level of H3K79 methylation also increases the radiosensitivity of mammalian cells. Recent evidence suggests that knocking-out of Dot1L in mouse embryonic fibroblasts leads to a UV hypersensitivity and deficiency of transcription initiation [82]. Tumor cells with reduced H3K79 methylation show increased chromosomal instability and are more sensitive to γ-irradiation [83]. We speculate that the low level of H3K79 methylation may impair NHEJ repair and thus increases cellular radiosensitivity.

2.2.5. H4K20

Selective binding of 53BP1 to H4K20me2 at DSB sites is a significant and central determinant of NHEJ repair [84,85]. After irradiation, multiple myeloma SET domain containing protein (MMSET) is recruited to DSB sites in an ATM-dependent manner in order to methylate H4K20 and facilitate the recruitment of 53BP1 [86]. Then 53BP1 recruits the downstream effectors RIF1 and MAD2L2 to DSB sites and promotes NHEJ repair in G1-phase cells [87–89]. The content of newly generated H4K20me2 remains at a low level in S-phase, so the recruitment of 53BP1-RIF1-MAD2L2 complex mainly occurs on the pre-replicative chromatin with abundant of H4K20me2 [90,91]. After binding with H4K20me2, 53BP1 can promote the next stage of NHEJ repair.

Considering the importance of H4K20 methylation in NHEJ, the deficiency of H4K20 methylation may hinder DNA damage repair and increase cellular radiosensitivity. Li et al. (2016) [92] show that the deficiency of H4K20me1 leads to the accumulation of DNA damage and ATR-dependent cell cycle arrest. Since SUV4-20 catalyzes the di- and tri-methylation of lysine 20 on histone H4 (H4K20me2/3) [93], inhibition of SUV4-20 decreases 53BP1 foci formation upon ionizing radiation and reduces NHEJ-mediated DNA damage repair [94]. These studies indicate that the methylation of H4K20 are imperative for mediating cellular radiosensitivity.

2.3. Role of histone methylation in regulating the expression of DNA repair genes

2.3.1. H3K4

The level of H3K4me3 may also been increased after the incidence of DSBs [95]. Cells lacking H3K4me3 are defective in DSB repair through NHEJ pathway and challenge to survive in the presence of replication stresses [11]. This process is related to the SET domain proteins that can be used as histone methyltransferase to mediate H3K4 methylation and maintain genomic stability by activating the expression of DNA repair gene [11,96]. Deficiency of methyltransferase SET and MYND domain containing 3 (SMYD3) may cause a decrease of H3K4me3 [97]. Moreover, SMYD3 can create an active histone marker of the promoters of HR genes, such as MDC1 and EXO1, for transcription to improve the capacity of HR [97].

Loss of H3K4 methyltransferase SETD1A in hematopoietic stem cells (HSCs) leads to a low level of H3K4 methylation and deregulates DNA repair-related proteins [98]. SETD1A is crucial for DNA repair after irradiation and confers to radioresistance *in vivo* [98], Therefore, the elevation of H3K4 methylation leads to radioresistance by promoting DNA damage responses and activating transcriptional genes of DNA repair (Fig. 1).

2.3.2. H3K27

Similar to H3K9 methylation, the increase of H3K27 methylation can inhibit transcription and help to form compacted chromatin [99,100]. DNA damage can also lead to the demethylation of H3K27. Upon exposure to ionizing radiation, the histone demethylases UTX and JMJD3 can be recruited to DNA damage sites and then decrease the methylation of H3K27 and facilitate the

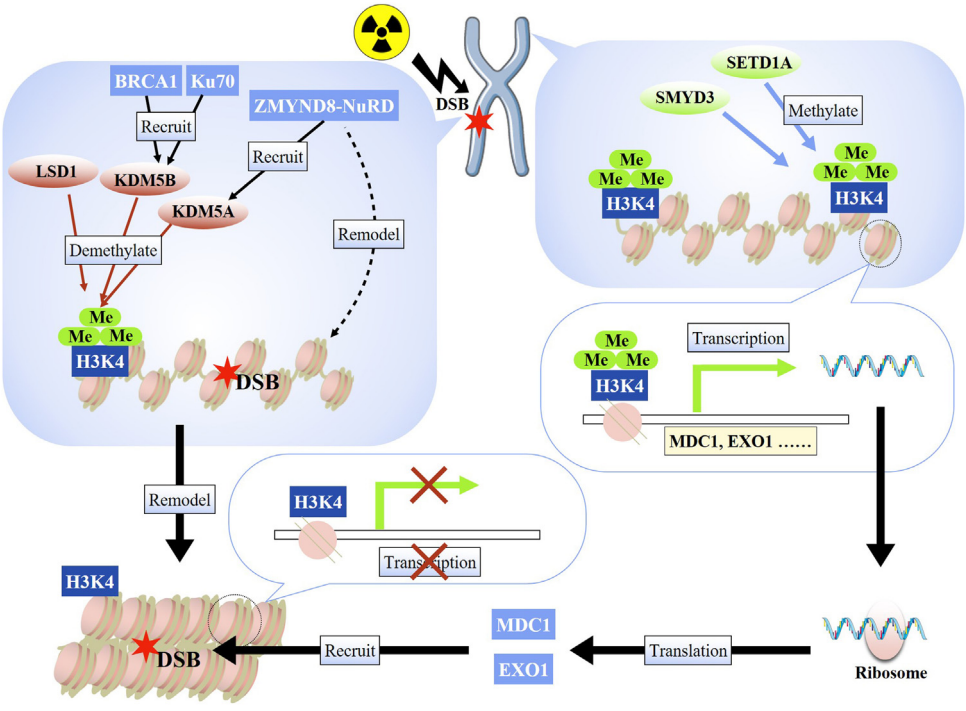

Fig. 1. The process of H3K4 methylation in DNA damage repair. After DSBs occurrence, the bidirectional changes of H3K4 methylation promote DNA repair process. Demethylases of KDM5B, KDM5A and LSD1 are recruited to DSB sites to mediate the demethylation of H3K4. KDM5B recruits Ku70 and BRCA1 to promote DSB repair. KDM5A recruits the ZMYND8-NuRD complex and regulates chromatin remodeling to repress transcription. On the other hand, histone methyltransferases SMYD3 and SETD1A can increase H3K4 methylation and promote the transcription of DNA repair genes such as MDC1 and EXO1. After translation in extranuclear, the newly generated MDC1 and EXO1 can be recruited into nucleus to participate in DNA damage repair.

expression of specific proteins, such as Ku80, a vital mediator of NHEJ pathway, in a p53-dependent manner [101,102]. Knockdown of UTX could increase the level of H3K27me3 and enhances the cellular radiosensitivity of tumor cells [103].

2.4. Role of histone methylation in mediating the dynamic change of chromatin

2.4.1. H3K4

When DSB occurs, chromatin needs to be remodeled to promote DNA damage repair. Upon DSBs, the demethylation of H3K4 at DNA damage sites is an important step for the transition of compacted chromatin [41,104]. KDM5A can be recruited to DSB sites and demethylates H3K4me3, which contributes to the recruitment of ZMYND8–NuRD complex [104]. This complex further regulate chromatin remodeling to repress transcription and promotes HR repair [105]. The remodeled chromatin with a compact spatial structure protects the damaged DNA from degradation (Fig. 1) [8]. Accordingly, the H3K4 demethylation plays an important role in radiation response and the abnormally high level of H3K4 methylation may impair chromatin remodeling and make cells radiosensitive.

2.4.2. H3K9

H3K9 methylation can be dynamically altered during DNA repair process. After DSBs induction, the spatial structure of chromatin becomes compact at first and then is relaxed [36] together with the changes of H3K9 methylation during DNA repair [106] (Fig. 2). In general, the methylation of H3K9 is required for the formation of compacted chromatin and the recruitment of DNA repair-related proteins, while the demethylation of H3K9 increases chromatin accessibility and facilitates DSB end resection [95] (Fig. 2). Since H3K9 methylation can be dynamically changed upon irradiation, both aberrantly high and low levels of H3K9 methylation could block the DNA repair process and increase cellular radiosensitivity.

Generally, H3K9 methylation can also regulate cell response to radiation by interacting with DNA repair-related proteins. Shortly after irradiation, the KAP-1/HP1/SUV39H1 complex rapidly bind to chromatin at DSB sites to activates Tip60 and then transiently increases the methylation of H3K9 [107]. SUV39H1 can trimethylate H3K9 and recruit HP1. Increased H3K9me3 and HP1 help to form repressive chromatin structure that has functions of inhibiting transcription and preventing damaged DNA from degradation [8]. Additionally, DNA damage-induced compact chromatin helps to recruit DNA repair-related proteins and promotes DNA repair process. For instance, the MRN complex can identify H3K9me3 and activate Tip60 [108]. Tip60 is responsible for the activation of ATM [109] that triggers the release of KAP-1/HP1/SUV39H1 complex from DNA damage site [107] and activates HR repair pathway. Also, histone methyltransferase SETDB1 can catalyze the formation of H3K9me3 and promote DNA repair process [110]. Meanwhile, BARD1, another important DNA repair-related protein, can recognize H3K9me2 and recruit BRCA1 to promote HR repair at DSB sites [19,111]. These findings suggest that H3K9 methylation is vital and indispensable to DSB repair.

Considering the critical role of H3K9 methylation in DSB repair, some researches demonstrate that high-level H3K9 methylation is related to radioresistance. For instance, H3K9me3 interacts with DNA repair-related proteins such as Chk1. Depending on the H3K9me3/S10p, a chromatin marker, overexpression of Chk1 contributes to poor prognosis and radioresistance in triple-negative breast cancer [112]. Moreover, SUV39h1 is a methyltransferase of H3K9 and also relates to DNA repair-related proteins. Cells lacking SUV39h1 have defective activation of Tip60 and ATM

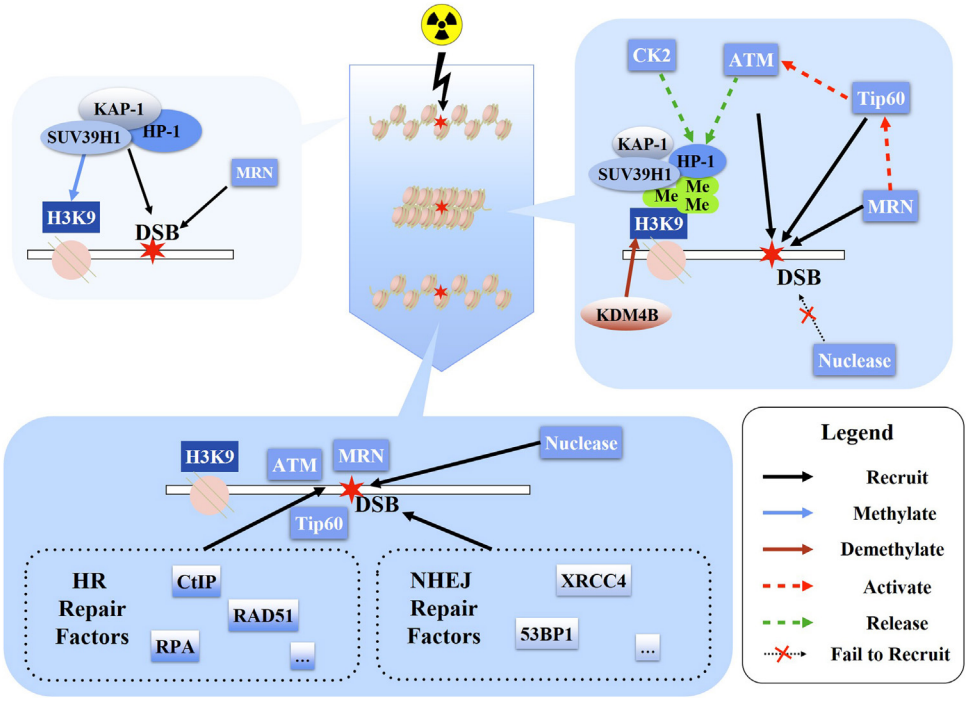

Fig. 2. The process of H3K9 methylation in DNA damage repair. After the incidence of DNA damage, chromatin structure undergoes compact at first and subsequently becomes relaxation where H3K9 methylation is involved. The KAP-1/HP-1/SUV39H1 complex is recruited to DSB sites to mediate the trimethylation of H3K9 as well as the formation of a temporary state of compacted chromatin which protects the broken ends of DNA from nucleases. The MRN complex can also be recruited to DSB sites and protect DNA ends. After binding to DSB sites, the SUV39H1 and MRN complex activates Tip60 and its downstream ATM. The activated ATM enables the release of KAP-1/HP-1/SUV39H1 complex from chromatin. KDM4B and CK2 interact with H3K9me3 and HP-1 to assist the relaxation of compact chromatin. At this time, nuclease can mediate the resection of DSBs. Meanwhile, the HR and NHEJ DNA repair-related proteins could be recruited to DSB sites and further activate their downstream signaling pathways to complete DNA damage repair.

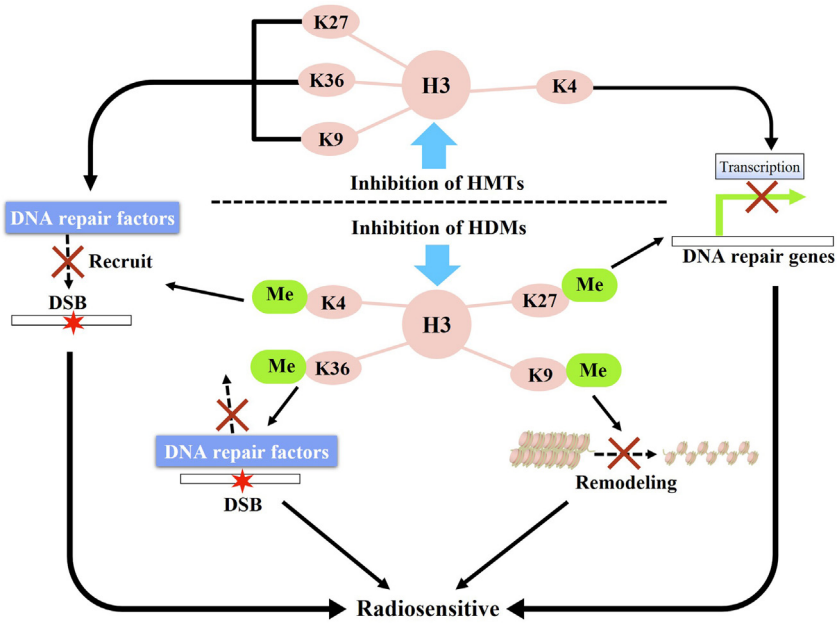

Fig. 3. The primary process of histone methylation in radiosensitivity. Histone methylation has a bidirectional effect on cellular radiosensitivity. Inhibition of HMTs results in the decrease of histone methylation level, while inhibition of HDMs fails to demethylate histone. The low methylation levels of H3K9, H3K27 and H3K36 together with the high methylation level of H3K4 may repress DNA repair-related protein recruitment. The high methylation level of H3K27 and low methylation level of H3K4 may repress the expression of DNA repair genes. The high methylation level of H3K9 may repress chromatin remodeling. The high methylation level of H3K36 may block the subsequent movement of DNA repair-related proteins. Accordingly, the histone methylation levels have dynamical changes during DNA repair processes, and the blockage of these changes may make cells sensitive to radiation.

together with the decreased H3K9me3 level and DSB repair ability [113,114], and hence have a high radiosensitivity.

Interestingly, some studies have come to a very different conclusion, showing that high-level H3K9 methylation contributes to DNA repair impairing and has a radiosensitizion effect. High-level H3K9 methylation could induce the formation of aberrantly compacted chromatin and then decrease radioresistance by inhibiting the functions of DNA damage repair. After transient upregulation, the H3K9 methylation can be rapidly decreased probably due to the expression of KDM4B [115]. Upon irradiation, the activated ATM can activate tumor suppressor p53. While maintaining genomic stability, p53 can inhibit SUV39H1 and thereby reduce the methylation of H3K9 [116,117]. The demethylation of H3K9 is involved in the rapid formation of open chromatin structure at DSBs. Meanwhile, after being recruited to DSB sites, HP1 can bind to H3K9me3 and maintain the stability of compacted chromatin [118,119]. The casein kinase 2 (CK2) can mediate HP1′s dissociation from H3K9me3 and promotes chromatin relaxation [120,121]. The open chromatin structure makes the damaged DNA accessible for DNA repair-related proteins and hence promotes HR and NHEJ repair [31]. Inhibition of KDM4B results in aberrant hypermethylation of H3K9 at DSB sites, blocks HR repair process, induces the formation of DSBs, and thus potently sensitizes tumor cells to irradiation [106,122].

A chromatin compaction regulator SPOC1 can interact with H3K9 methyltransferases and then enhances H3K9 trimethylation [123]. SPOC1 depletion results in a decrease of H3K9me3 and enhances 53BP1 foci formation, NHEJ repair activity, and cellular radioresistance [123]. Overexpression of SPOC1 may increase H3K9 methylation and fail to relax heterochromatin [123,124]. Generally, the hypermethylation of H3K9 may reduce the ability of DNA repair by forming compact chromatin structure and blocking the subsequent DNA repair process.

2.5. Role of histone methylation in other types of DNA damage

DNA damage repair includes base excision repair (BER), mismatch repair (MMR), nucleotide excision repair (NER), and DSB repair [125]. Histone methylation also plays an important role in other types of DNA damage repair besides DSB repair. Cells deficient in BER exhibit perturbations in global levels of histone methylation, including increase of histone H3K4me2/3 and decrease of H3K9me2 [126,127]. H3K36me3 is vital for the recruitment of MutSα, a core of MMR repair. Therefore, cells lacking H3K36 tri-methyltransferase SETD2 are deficient in MMR and display an elevated spontaneous mutation frequency [128]. Moreover, H3K79 methylation is required for efficient NER. Loss of H3K79 methylation may impair the expression of Rad16 (ortholog of human XPF, a core of NER repair) in yeast and leads the cells sensitive to UV radiation [129]. Although current studies have focused on the effect of histone methylation on DSB repair, further investigations of the relationship between histone methylation and other types of DNA repair may provide new insights for the functions of histone methylation in cellular radiosensitivity.

3. The role of histone methylation in radiotherapy

3.1. New molecular markers of cancer prognosis

Histone methylation plays a key role in tumorigenesis. The regulation of histone methylation is associated with the development of various cancers, such as gastric cancer, liver cancer, pancreatic cancer, and colorectal cancer [130]. In other words, there is a significant difference in the level of histone methylation between normal and tumor cells. Therefore, the level of histone methylation can be applied as the molecular markers of cancer prognosis. As noted by Kidder, the low level of H3K4 methylation

always leads to poor prognosis, probably by inhibiting the expression of tumor suppressor genes BRCA1, CAV1, and HOXA5 [42]. Based on the ability of H3K9me3 in inhibiting the expression of tumor suppressor genes [131], the activation of SUV39H1 and the increase of H3K9me3 may play an indispensable roles in tumorigenesis of gastric carcinoma [132]. Besides, the formation of H3K9me3 in the E-cadherin promoter may induce lung epithelial-mesenchymal transition after irradiation [133]. H3K27me3 elevation is also reported to be associated with the poor prognosis of esophageal squamous [134].

There is plenty of evidence shows that some HMTs and HDMs can be used as tumor prognosis biomarkers. For example, the overexpression of KDM5B predicts a poor prognosis in the patients with head and neck squamous cell carcinomas [135], the overexpression of LSD1 predicts poor prognosis of gastric cancer [136], and the elevation of UTX is associated with poor prognosis of breast cancer [137]. Due to the different histone methylation levels between tumor and normal tissues, histone methylation holds tremendous promise for the diagnosis of cancer.

3.2. Potential therapeutic targets for radiosensitizer

Considering the indispensable role of histone methylation in cancer prognosis, the development of novel drugs targeting HMTs and HDMs has received great attentions, where H3K4 demethylases are currently a major target of radiosensitizer. For instance, KDM5A plays a vital role in cancer processes including tumorigenesis, metastasis, and drug tolerance, and thus has been suggested to be a potential cancer therapeutic target [138]. A novel inhibitor of KDM5A, Jumonji inhibitor, can increase H3K4 methylation at DSBs, impair DNA damage repair, and overcome radioresistance in lung cancer [43]. Moreover, the inhibition of KDM5B can suppress tumor cell invasion and promote cell death after irradiation [139,140].

Besides H3K4, HMTs and HDMs can also be targeted for radiosensitization. A previous study find that the inhibitor of EZH2 can increase γH2AX foci after irradiation and increase cellular radiosensitivity in prostate cancer [141]. Histone demethylases of H3K9, KDM4B and KDM4D are also associated with radioresistance [142]. In addition, the inhibitor of H4K20 methylation could be applied as a DNA repair-based drug of tumor therapy [94]. During the development of tumors, histone methylation patterns are dramatically changed in comparison with normal tissues. Therefore, we suggest that the inhibitors of HMTs and HDMs are potential candidates of new radiosensitizers for radiotherapy.

Unfortunately, so far most reports concerning the regulatory function of histone methylation concentrate in radiotherapy for killing tumor cells [143], while radiation-induced histone methylation is rarely studied in normal tissue. Further researches on the role of histone methylation in radiation damage of normal tissues may ensure the clinical safety of anti-tumor drugs based on histone methylation regulation.

4. Conclusions and perspectives

Histone methylation plays an essential role in regulating gene expression and chromatin remodeling, it provides the binding sites for DNA repair-related proteins and hence is involved in DNA repair processes. But the effect of histone methylation on radiosensitivity is bidirectional and complicated due to its multiple functions. Even the same type of histone methylation could lead to either radiation tolerance or radiosensitization effect, which is regulated by different genes. According to the study of Arndt et al. [98], H3K4 methyltransferase SETD1A could increase radioresistance by upregulating the expression of DNA repair-related proteins RAD51, Bre and FANCD2 by promoting H3K4 methylation. However, H3K4 demethylation is also helpful in recruiting DNA repair-related proteins and promotes DNA repair upon irradiation [43,47,48].

The methylation and demethylation of H3K9 also have indispensable linkage in the DNA repair process after irradiation [36]. The lack of H3K9 methyltransferase SUV39H1 leads to a low level of H3K9me3 and increases cellular radiosensitivity [113,114]. However, inhibition of H3K9 demethylase KDM4B results in hypermethylation of H3K9 and potently sensitizes cells to irradiation [106,122].

Besides, H3K27me3 can promote HR repair by providing binding sites for nuclease MUS81 [51,52] but inhibits the expression of Ku80 and thus blocks NHEJ repair [101,102]. H3K36 methylation can promote the recruitment of DNA repair-related proteins and hence makes cells to be resistant to radiation [62,63]. However, the demethylation of H3K36 is also a fundamental step in DNA damage repair [72].

Histone methylation has complex effects on cellular radiosensitivity due to its dynamical response to DNA damage. After the incidence of radiation-induced DNA damage, histone methylation needs to undergo dynamic changes under the action of HMTs and HDMs to complete DNA repair. Thus, the mechanisms of histone methylation regulated cellular radiosensitivity are classical i.e., the blockage of DNA repair process increases cellular radiosensitivity and the promotion of DNA repair results in radioresistance. The inhibition of HMTs and HDMs may hinder the change of histone methylation, impair the DNA repair process, and sensitize cells to radiation (Fig. 3). Up-regulation and down-regulation of histone methylation at the same site may lead to the increase of radiosensitivity, mainly because histone methylation is changed under different HMTs and HDMs. For example, inhibition of histone demethylases, such as KDM5B, can block H3K4 demethylation, impair DNA repair, and increase cellular radiosensitivity [41]. On the other hand, some HMTs, such as SETD1A and SMYD3, can increase H3K4 methylation and promote the transcription and expression of DNA repair genes and ultimately lead to radioresistance [97,98].

Generally, affected by different HMTs and HDMs, histone methylation has dual effects on cellular radiosensitivity i.e., it allows cells to be either radiosensitive or radioresistant under different circumstances. After irradiation, HMTs and HDMs can regulate the level of histone methylation to affect the recruitment of DNA repair-related proteins, the expression of DNA repair genes, the dynamic change of chromatin, and finally affect cellular radiosensitivity.

Collectively, the effects of histone methylation on cellular radiosensitivity can be summarized as follow: histone methylation maybe an intermediate linkage in the regulation of DNA repair, while the HMTs and HDMs are the upstream in regulating cellular radiosensitivity. Although both aberrantly high and low levels of histone methylation could increase cellular radiosensitivity, HMTs and HDMs do not show a dual effect on cellular radiosensitivity. In other words, it is HMTs and HDMs rather than histone methylation itself that could fundamentally regulate cellular radiosensitivity. Histone methylation is more of a tool through which HMTs and HDMs can influence cell response to radiation. The inhibitors targeting HMTs and HDMs, such as Jumonji inhibitors, may become new sensitizers for tumor radiotherapy [43]. Further study of the relationship between histone methylation and cellular radiosensitivity may provide deep insights in developing new strategy of radiotherapy.

Declaration of Competing Interest

The authors report no declarations of interest.

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References

[1] J.M. Borras, Y. Lievens, P. Dunscombe, M. Coffey, J. Malicki, J. Corral, et al., The optimal utilization proportion of external beam radiotherapy in European countries: an ESTRO-HERO analysis, Radiother. Oncol. 116 (2015) 38–44, doi:http://dx.doi.org/10.1016/j.radonc.2015.04.018.
[2] L. Galluzzi, J.M. Bravo-San Pedro, S. Demaria, S.C. Formenti, G. Kroemer, Activating autophagy to potentiate immunogenic chemotherapy and radiation therapy, Nat. Rev. Clin. Oncol. 14 (2017) 247–258, doi:http://dx.doi.org/10.1038/nrclinonc.2016.183.
[3] A.V. Gudkov, E.A. Komarova, The role of p53 in determining sensitivity to radiotherapy, Nat. Rev. Cancer 3 (2003) 117–129, doi:http://dx.doi.org/10.1038/nrc992.
[4] N. Foray, M. Bourguignon, N. Hamada, Individual response to ionizing radiation, Mutat. Res. 770 (2016) 369–386, doi:http://dx.doi.org/10.1016/j.mrrev.2016.09.001.
[5] H. Nikjoo, S. Uehara, W.E. Wilson, M. Hoshi, D.T. Goodhead, Track structure in radiation biology: theory and applications, Int. J. Radiat. Biol. 73 (1998) 355–364, doi:http://dx.doi.org/10.1080/095530098142176.
[6] W.L. Santivasi, F. Xia, Ionizing radiation-induced DNA damage, response, and repair, Antioxid. Redox Signal. 21 (2014) 251–259, doi:http://dx.doi.org/10.1089/ars.2013.5668.
[7] E.L. Greer, Y. Shi, Histone methylation: a dynamic mark in health, disease and inheritance, Nat. Rev. Genet. 13 (2012) 343–357, doi:http://dx.doi.org/10.1038/nrg3173.
[8] O. Gursoy-Yuzugullu, N. House, B.D. Price, Patching broken DNA: nucleosome dynamics and the repair of DNA breaks, J. Mol. Biol. 428 (2016) 1846–1860, doi:http://dx.doi.org/10.1016/j.jmb.2015.11.021.
[9] T. Kouzarides, Chromatin modifications and their function, Cell 128 (2007) 693–705, doi:http://dx.doi.org/10.1016/j.cell.2007.02.005.
[10] R. Li, X. Wei, D. Jiang, Protein methylation functions as the posttranslational modification switch to regulate autophagy, Cell. Mol. Life Sci. 76 (2019) 3711–3722, doi:http://dx.doi.org/10.1007/s00018-019-03161-x.
[11] M. Freitag, Histone methylation by SET domain proteins in fungi, Annu. Rev. Microbiol. 71 (2017) 413–439, doi:http://dx.doi.org/10.1146/annurev-micro-102215-095757.
[12] S.N. Powell, L.A. Kachnic, Roles of BRCA1 and BRCA2 in homologous recombination, DNA replication fidelity and the cellular response to ionizing radiation, Oncogene 22 (2003) 5784–5791, doi:http://dx.doi.org/10.1038/sj.onc.1206678.
[13] X. Li, W. Heyer, Homologous recombination in DNA repair and DNA damage tolerance, Cell Res. 18 (2008), doi:http://dx.doi.org/10.1038/cr.2008.1.
[14] Q. Liu, K. Lopez, J. Murnane, T. Humphrey, M.H. Barcellos-Hoff, Misrepair in context: TGFβ regulation of DNA repair, Front. Oncol. 9 (2019) 799, doi:http://dx.doi.org/10.3389/fonc.2019.00799.
[15] Z. Zhu, W. Chung, E.Y. Shim, S.E. Lee, G. Ira, Sgs1 helicase and two nucleases Dna2 and Exo1 resect DNA double-strand break ends, Cell 134 (2008) 981–994, doi:http://dx.doi.org/10.1016/j.cell.2008.08.037.
[16] A.A. Sartori, C. Lukas, J. Coates, M. Mistrik, S. Fu, J. Bartek, et al., Human CtIP promotes DNA end resection, Nature 450 (2007) 509–514, doi:http://dx.doi.org/10.1038/nature06337.
[17] K. Kaniecki, L. De Tullio, E.C. Greene, A change of view: homologous recombination at single-molecule resolution, Nat. Rev. Genet. 19 (2018) 191–207, doi:http://dx.doi.org/10.1038/nrg.2017.92.
[18] A.V. Nimonkar, J. Genschel, E. Kinoshita, P. Polaczek, J.L. Campbell, C. Wyman, et al., BLM-DNA2-RPA-MRN and EXO1-BLM-RPA-MRN constitute two DNA end resection machineries for human DNA break repair, Genes Dev. 25 (2011) 350–362, doi:http://dx.doi.org/10.1101/gad.2003811.
[19] R. Prakash, Y. Zhang, W. Feng, M. Jasin, Homologous recombination and human health: the roles of BRCA1, BRCA2, and associated proteins, Cold Spring Harb. Perspect. Biol. 7 (2015)a016600, doi:http://dx.doi.org/10.1101/cshperspect.a016600.
[20] A. Mehta, J.E. Haber, Sources of DNA double-strand breaks and models of recombinational DNA repair, Cold Spring Harb. Perspect. Biol. 6 (2014) a016428, doi:http://dx.doi.org/10.1101/cshperspect.a016428.
[21] C.W. Langberg, M. Hauer-Jensen, C.C. Sung, C.J. Kane, Expression of fibrogenic cytokines in rat small intestine after fractionated irradiation, Radiother. Oncol. 32 (1994) 29–36, doi:http://dx.doi.org/10.1016/0167-8140(94)90446-4.
[22] M. Jasin, R. Rothstein, Repair of strand breaks by homologous recombination, Cold Spring Harb. Perspect. Biol. 5 (2013)a012740, doi:http://dx.doi.org/10.1101/cshperspect.a012740.
[23] W.D. Wright, S.S. Shah, W. Heyer, Homologous recombination and the repair of DNA double-strand breaks, J. Biol. Chem. 293 (2018) 10524–10535, doi:http://dx.doi.org/10.1074/jbc.TM118.000372.
[24] L. Centurione, F.B. Aiello, DNA repair and cytokines: TGF-β, IL-6, and Thrombopoietin as different biomarkers of Radioresistance, Front. Oncol. 6 (2016) 175, doi:http://dx.doi.org/10.3389/fonc.2016.00175.
[25] W.S. Dynan, S. Yoo, Interaction of Ku protein and DNA-dependent protein kinase catalytic subunit with nucleic acids, Nucleic Acids Res. 26 (1998) 1551–1559, doi:http://dx.doi.org/10.1093/nar/26.7.1551.
[26] C. Wang, S.P. Lees-Miller, Detection and repair of ionizing radiation-induced DNA double strand breaks: new developments in nonhomologous end joining, Int. J. Radiat. Oncol. Biol. Phys. 86 (2013) 440–449, doi:http://dx.doi.org/10.1016/j.ijrobp.2013.01.011.
[27] Y. Ma, U. Pannicke, K. Schwarz, M.R. Lieber, Hairpin opening and overhang processing by an Artemis/DNA-dependent protein kinase complex in nonhomologous end joining and V(D)J recombination, Cell 108 (2002) 781–794, doi:http://dx.doi.org/10.1016/s0092-8674(02)00671-2.
[28] B.L. Mahaney, K. Meek, S.P. Lees-Miller, Repair of ionizing radiation-induced DNA double-strand breaks by non-homologous end-joining, Biochem. J. 417 (2009) 639–650, doi:http://dx.doi.org/10.1042/BJ20080413.
[29] A. Xie, A. Hartlerode, M. Stucki, S. Odate, N. Puget, A. Kwok, et al., Distinct roles of chromatin-associated proteins MDC1 and 53BP1 in mammalian double-strand break repair, Mol. Cell 28 (2007) 1045–1057, doi:http://dx.doi.org/10.1016/j.molcel.2007.12.005.
[30] F. Ochs, K. Somyajit, M. Altmeyer, M.-B. Rask, J. Lukas, C. Lukas, 53BP1 fosters fidelity of homology-directed DNA repair, Nat. Struct. Mol. Biol. 23 (2016) 714–721, doi:http://dx.doi.org/10.1038/nsmb.3251.
[31] B.D. Price, A.D. D'Andrea, Chromatin remodeling at DNA double-strand breaks, Cell 152 (2013) 1344–1354, doi:http://dx.doi.org/10.1016/j.cell.2013.02.011.
[32] M.J. Smerdon, M.W. Lieberman, Nucleosome rearrangement in human chromatin during UV-induced DNA- reapir synthesis, Proc. Natl. Acad. Sci. U. S. A. 75 (1978) 4238–4241, doi:http://dx.doi.org/10.1073/pnas.75.9.4238.
[33] J. Tang, N.W. Cho, G. Cui, E.M. Manion, N.M. Shanbhag, M.V. Botuyan, et al., Acetylation limits 53BP1 association with damaged chromatin to promote homologous recombination, Nat. Struct. Mol. Biol. 20 (2013) 317–325, doi:http://dx.doi.org/10.1038/nsmb.2499.
[34] X. Jiang, Y. Xu, B.D. Price, Acetylation of H2AX on lysine 36 plays a key role in the DNA double-strand break repair pathway, FEBS Lett. 584 (2010) 2926–2930, doi:http://dx.doi.org/10.1016/j.febslet.2010.05.017.
[35] T. Ikura, S. Tashiro, A. Kakino, H. Shima, N. Jacob, R. Amunugama, et al., DNA damage-dependent acetylation and ubiquitination of H2AX enhances chromatin dynamics, Mol. Cell. Biol. 27 (2007) 7028–7040, doi:http://dx.doi.org/10.1128/MCB.00579-07.
[36] D.M. Chou, B. Adamson, N.E. Dephoure, X. Tan, A.C. Nottke, K.E. Hurov, et al., A chromatin localization screen reveals poly (ADP ribose)-regulated recruitment of the repressive polycomb and NuRD complexes to sites of DNA damage, Proc. Natl. Acad. Sci. U. S. A. 107 (2010) 18475–18480, doi:http://dx.doi.org/10.1073/pnas.1012946107.
[37] N.M. Shanbhag, I.U. Rafalska-Metcalf, C. Balane-Bolivar, S.M. Janicki, R.A. Greenberg, ATM-dependent chromatin changes silence transcription in cis to DNA double-strand breaks, Cell 141 (2010) 970–981, doi:http://dx.doi.org/10.1016/j.cell.2010.04.038.
[38] T. Pankotai, C. Bonhomme, D. Chen, E. Soutoglou, DNAPKcs-dependent arrest of RNA polymerase II transcription in the presence of DNA breaks, Nat. Struct. Mol. Biol. 19 (2012) 276–282, doi:http://dx.doi.org/10.1038/nsmb.2224.
[39] T. Pankotai, E. Soutoglou, Double strand breaks: hurdles for RNA polymerase II transcription? Transcription 4 (2013) 34–38, doi:http://dx.doi.org/10.4161/trns.22879.
[40] F. Aymard, B. Bugler, C.K. Schmidt, E. Guillou, P. Caron, S. Briois, et al., Transcriptionally active chromatin recruits homologous recombination at DNA double-strand breaks, Nat. Struct. Mol. Biol. 21 (2014) 366–374, doi:http://dx.doi.org/10.1038/nsmb.2796.
[41] X. Li, L. Liu, S. Yang, N. Song, X. Zhou, J. Gao, et al., Histone demethylase KDM5B is a key regulator of genome stability, Proc. Natl. Acad. Sci. U. S. A. 111 (2014) 7096–7101, doi:http://dx.doi.org/10.1073/pnas.1324036111.
[42] B. Xhabija, B.L. Kidder, KDM5B is a master regulator of the H3K4-methylome in stem cells, development and cancer, Semin. Cancer Biol. 57 (2019) 79–85, doi:http://dx.doi.org/10.1016/j.semcancer.2018.11.001.
[43] J. Bayo, T.A. Tran, L. Wang, S. Peña-Llopis, A.K. Das, E.D. Martinez, Jumonji inhibitors overcome radioresistance in Cancer through changes in H3K4 methylation at double-strand breaks, Cell Rep. 25 (2018) 1040–1050, doi:http://dx.doi.org/10.1016/j.celrep.2018.09.081 e5.
[44] S. Pippa, C. Manironi, V. Licursi, L. Bombardi, G. Colotti, E. Cundari, et al., Small molecule inhibitors of KDM5 histone demethylases increase the radiosensitivity of breast Cancer cells overexpressing JARID1B, Molecules 24 (2019), doi:http://dx.doi.org/10.3390/molecules24091739.
[45] C. Penterling, G.A. Drexler, C. Böhland, R. Stamp, C. Wilke, H. Braselmann, et al., Depletion of histone demethylase Jarid1A resulting in histone hyperacetylation and radiation sensitivity does not affect DNA double-strand break repair, PLoS One 11 (2016), doi:http://dx.doi.org/10.1371/journal.pone.0156599 e0156599.
[46] B. Peng, J. Wang, Y. Hu, H. Zhao, W. Hou, H. Zhao, et al., Modulation of LSD1 phosphorylation by CK2/WIP1 regulates RNF168-dependent 53BP1 recruitment in response to DNA damage, Nucleic Acids Res. 43 (2015) 5936–5947, doi:http://dx.doi.org/10.1093/nar/gkv528.
[47] N. Mosammaparast, H. Kim, B. Laurent, Y. Zhao, H.J. Lim, M.C. Majid, et al., The histone demethylase LSD1/KDM1A promotes the DNA damage response, J. Cell Biol. 203 (2013) 457–470, doi:http://dx.doi.org/10.1083/jcb.201302092.

[48] M. Wojtala, A. Dąbek, D. Rybaczek, A. Śliwińska, E. Świderska, K. Słapek, et al., Silencing Lysine-Specific Histone Demethylase 1 (LSD1) causes increased HP1-positive chromatin, stimulation of DNA repair processes, and dysregulation of proliferation by Chk1 phosphorylation in human endothelial cells, Cells 8 (2019), doi:http://dx.doi.org/10.3390/cells8101212.
[49] R. Margueron, D. Reinberg, The Polycomb complex PRC2 and its mark in life, Nature 469 (2011) 343–349, doi:http://dx.doi.org/10.1038/nature09784.
[50] C. Martin, Y. Zhang, The diverse functions of histone lysine methylation, Nat. Rev. Mol. Cell Biol. 6 (2005) 838–849, doi:http://dx.doi.org/10.1038/nrm1761.
[51] B. Rondinelli, E. Gogola, H. Yücel, A.A. Duarte, M. van de Ven, R. van der Sluijs, et al., EZH2 promotes degradation of stalled replication forks by recruiting MUS81 through histone H3 trimethylation, Nat. Cell Biol. 19 (2017) 1371–1378, doi:http://dx.doi.org/10.1038/ncb3626.
[52] S. Campbell, I.H. Ismail, L.C. Young, G.G. Poirier, M.J. Hendzel, Polycomb repressive complex 2 contributes to DNA double-strand break repair, Cell Cycle 12 (2013) 2675–2683, doi:http://dx.doi.org/10.4161/cc.25795.
[53] Y. Zhang, J.F. Chang, J. Sun, L. Chen, X.M. Yang, H.Y. Tang, et al., Histone H3K27 methylation modulates the dynamics of FANCD2 on chromatin to facilitate NHEJ and genome stability, J. Cell. Sci. 131 (2018), doi:http://dx.doi.org/10.1242/jcs.215525.
[54] S. Gao, K. Li, H. Qiu, L. Zhu, C. Pan, Y. Zhao, et al., Enhancing chemotherapy sensitivity by targeting PcG via the ATM/p53 pathway, Am. J. Cancer Res. 7 (2017) 1874–1883.
[55] J. Tan, X. Yang, L. Zhuang, X. Jiang, W. Chen, P.L. Lee, et al., Pharmacologic disruption of Polycomb-repressive complex 2-mediated gene repression selectively induces apoptosis in cancer cells, Genes Dev. 21 (2007) 1050–1063, doi:http://dx.doi.org/10.1101/gad.1524107.
[56] I. Alimova, D.K. Birks, P.S. Harris, J.A. Knipstein, S. Venkataraman, V.E. Marquez, et al., Inhibition of EZH2 suppresses self-renewal and induces radiation sensitivity in atypical rhabdoid teratoid tumor cells, Neuro. Oncol. 15 (2013) 149–160, doi:http://dx.doi.org/10.1093/neuonc/nos285.
[57] X. Ma, J. Zhou, J. Liu, G. Wu, Y. Yu, H. Zhu, et al., LncRNA ANCR promotes proliferation and radiation resistance of nasopharyngeal carcinoma by inhibiting PTEN expression, Onco. Targets. Ther. 11 (2018) 8399–8408, doi:http://dx.doi.org/10.2147/OTT.S182573.
[58] A. Sak, D. Kübler, K. Bannik, M. Groneberg, S. Strunz, R. Kriehuber, et al., Epigenetic silencing and activation of transcription: influence on the radiation sensitivity of glioma cell lines, Int. J. Radiat. Biol. 93 (2017) 494–506, doi:http://dx.doi.org/10.1080/09553002.2017.1270472.
[59] M.Y. Cai, Z.T. Tong, W. Zhu, Z.Z. Wen, H.L. Rao, L.L. Kong, et al., H3K27me3 protein is a promising predictive biomarker of patients' survival and chemoradioresistance in human nasopharyngeal carcinoma, Mol. Med. 17 (2011) 1137–1145, doi:http://dx.doi.org/10.2119/molmed.2011.00054.
[60] S.H. Kim, K. Joshi, R. Ezhilarasan, T.R. Myers, J. Siu, C. Gu, et al., EZH2 protects glioma stem cells from radiation-induced cell death in a MELK/FOXM1-dependent manner, Stem Cell Rep. 4 (2015) 226–238, doi:http://dx.doi.org/10.1016/j.stemcr.2014.12.006.
[61] M. Daugaard, A. Baude, K. Fugger, L.K. Povlsen, H. Beck, C.S. Sørensen, et al., LEDGF (p75) promotes DNA-end resection and homologous recombination, Nat. Struct. Mol. Biol. 19 (2012) 803–810, doi:http://dx.doi.org/10.1038/nsmb.2314.
[62] S.X. Pfister, S. Ahrabi, L.P. Zalmas, S. Sarkar, F. Aymard, C.Z. Bachrati, et al., SETD2-dependent histone H3K36 trimethylation is required for homologous recombination repair and genome stability, Cell Rep. 7 (2014) 2006–2018, doi:http://dx.doi.org/10.1016/j.celrep.2014.05.026.
[63] K.E. Hacker, C.C. Fahey, S.A. Shinsky, Y.C.J. Chiang, J.V. DiFiore, D.K. Jha, et al., Structure/Function analysis of recurrent mutations in SETD2 protein reveals a critical and conserved role for a SET domain residue in maintaining protein stability and histone H3 Lys-36 trimethylation, J. Biol. Chem. 291 (2016) 21283–21295, doi:http://dx.doi.org/10.1074/jbc.M116.739375.
[64] S. Carvalho, A.C. Vítor, S.C. Sridhara, F.B. Martins, A.C. Raposo, J.M.P. Desterro, et al., SETD2 is required for DNA double-strand break repair and activation of the p53-mediated checkpoint, Elife 3 (2014) e02482, doi:http://dx.doi.org/10.7554/eLife.02482.
[65] S. Fnu, E.A. Williamson, L.P. De Haro, M. Brenneman, J. Wray, M. Shaheen, et al., Methylation of histone H3 lysine 36 enhances DNA repair by nonhomologous end-joining, Proc. Natl. Acad. Sci. U. S. A. 108 (2011) 540–545, doi:http://dx.doi.org/10.1073/pnas.1013571108.
[66] R. Hromas, E.A. Williamson, S. Fnu, Y.-J. Lee, S.-J. Park, B.D. Beck, et al., Chk1 phosphorylation of Metnase enhances DNA repair but inhibits replication fork restart, Oncogene 31 (2012) 4245–4254, doi:http://dx.doi.org/10.1038/onc.2011.586.
[67] S.H. Lee, M. Oshige, S.T. Durant, K.K. Rasila, E.A. Williamson, H. Ramsey, et al., The SET domain protein Metnase mediates foreign DNA integration and links integration to nonhomologous end-joining repair, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 18075–18080, doi:http://dx.doi.org/10.1073/pnas.0503676102.
[68] C.F. Chang, P.C. Chu, P.Y. Wu, M.Y. Yu, J.Y. Lee, M.D. Tsai, et al., PHRF1 promotes genome integrity by modulating non-homologous end-joining, Cell Death Dis. 6 (2015) e1716, doi:http://dx.doi.org/10.1038/cddis.2015.81.
[69] L.L. Cao, F. Wei, Y. Du, B. Song, D. Wang, C. Shen, et al., ATM-mediated KDM2A phosphorylation is required for the DNA damage repair, Oncogene 35 (2016) 301–313, doi:http://dx.doi.org/10.1038/onc.2015.81.
[70] W.L. Berry, R. Janknecht, KDM4/JMJD2 histone demethylases: epigenetic regulators in cancer cells, Cancer Res. 73 (2013) 2936–2942, doi:http://dx.doi.org/10.1158/0008-5472.CAN-12-4300.
[71] L. Duan, R.E. Perez, P.D. Chastain, M.T. Mathew, D.R. Bijukumar, C.G. Maki, JMJD2 promotes acquired cisplatin resistance in non-small cell lung carcinoma cells, Oncogene 38 (2019) 5643–5657, doi:http://dx.doi.org/10.1038/s41388-019-0814-6.
[72] P.G. Amendola, N. Zaghet, J.J. Ramalho, J. Vilstrup Johansen, M. Boxem, A.E. Salcini, JMJD-5/KDM8 regulates H3K36me2 and is required for late steps of homologous recombination and genome integrity, PLoS Genet. 13 (2017) e1006632, doi:http://dx.doi.org/10.1371/journal.pgen.1006632.
[73] S.Y. Hwang, K. Heo, J.S. Kim, J.W. Im, S.M. Lee, M. Cho, et al., Emodin attenuates radioresistance induced by hypoxia in HepG2 cells via the enhancement of PARP1 cleavage and inhibition of JMJD2B, Oncol. Rep. 33 (2015) 1691–1698, doi:http://dx.doi.org/10.3892/or.2015.3744.
[74] Y. Yao, W.Y. Zhou, R.X. He, Down-regulation of JMJD5 suppresses metastasis and induces apoptosis in oral squamous cell carcinoma by regulating p53/NF-κB pathway, Biomed. Pharmacother. 109 (2019) 1994–2004, doi:http://dx.doi.org/10.1016/j.biopha.2018.07.144.
[75] Z. Farooq, S. Banday, T.K. Pandita, M. Altaf, The many faces of histone H3K79 methylation, Mutat. Res. Rev. Mutat. Res. 768 (2016) 46–52, doi:http://dx.doi.org/10.1016/j.mrrev.2016.03.005.
[76] R. Wysocki, A. Javaheri, S. Allard, F. Sha, J. Côté, S.J. Kron, Role of Dot1-dependent histone H3 methylation in G1 and S phase DNA damage checkpoint functions of Rad9, Mol. Cell. Biol. 25 (2005) 8430–8443, doi:http://dx.doi.org/10.1128/MCB.25.19.8430-8443.2005.
[77] Y. Huyen, O. Zgheib, R.A. Ditullio, V.G. Gorgoulis, P. Zacharatos, T.J. Petty, et al., Methylated lysine 79 of histone H3 targets 53BP1 to DNA double-strand breaks, Nature 432 (2004) 406–411, doi:http://dx.doi.org/10.1038/nature03114.
[78] Y. Chen, W.G. Zhu, Biological function and regulation of histone and non-histone lysine methylation in response to DNA damage, Acta Biochim. Biophys. Sin. (Shanghai). 48 (2016) 603–616, doi:http://dx.doi.org/10.1093/abbs/gmw050.
[79] S. Zheng, D. Li, Z. Lu, G. Liu, M. Wang, P. Xing, et al., Bre1-dependent H2B ubiquitination promotes homologous recombination by stimulating histone eviction at DNA breaks, Nucleic Acids Res. 46 (2018) 11326–11339, doi:http://dx.doi.org/10.1093/nar/gky918.
[80] F. Conde, P.A. San-Segundo, Role of Dot1 in the response to alkylating DNA damage in Saccharomyces cerevisiae: regulation of DNA damage tolerance by the error-prone polymerases Polzeta/Rev1, Genetics. 179 (2008) 1197–1210, doi:http://dx.doi.org/10.1534/genetics.108.089003.
[81] S.B. Chernikova, J.A. Dorth, O.V. Razorenova, J.C. Game, J.M. Brown, Deficiency in Bre1 impairs homologous recombination repair and cell cycle checkpoint response to radiation damage in mammalian cells, Radiat. Res. 174 (2010) 558–565, doi:http://dx.doi.org/10.1667/RR2184.1.
[82] V. Oksenych, A. Zhovmer, S. Ziani, P.-O. Mari, J. Eberova, T. Nardo, et al., Histone methyltransferase DOT1L drives recovery of gene expression after a genotoxic attack, PLoS Genet. 9 (2013) e1003611, doi:http://dx.doi.org/10.1371/journal.pgen.1003611.
[83] Y.-H. Lin, P.M. Kakadia, Y. Chen, Y.-Q. Li, A.J. Deshpande, C. Buske, et al., Global reduction of the epigenetic H3K79 methylation mark and increased chromosomal instability in CALM-AF10-positive leukemias, Blood 114 (2009) 651–658, doi:http://dx.doi.org/10.1182/blood-2009-03-209395.
[84] B. Wang, S. Matsuoka, P.B. Carpenter, S.J. Elledge, 53BP1, a mediator of the DNA damage checkpoint, Science 298 (2002) 1435–1438, doi:http://dx.doi.org/10.1126/science.1076182.
[85] C.T. Tuzon, T. Spektor, X. Kong, L.M. Congdon, S. Wu, G. Schotta, et al., Concerted activities of distinct H4K20 methyltransferases at DNA double-strand breaks regulate 53BP1 nucleation and NHEJ-directed repair, Cell Rep. 8 (2014) 430–438, doi:http://dx.doi.org/10.1016/j.celrep.2014.06.013.
[86] H. Pei, L. Zhang, K. Luo, Y. Qin, M. Chesi, F. Fei, et al., MMSET regulates histone H4K20 methylation and 53BP1 accumulation at DNA damage sites, Nature 470 (2011) 124–128, doi:http://dx.doi.org/10.1038/nature09658.
[87] H. Zhang, H. Liu, Y. Chen, X. Yang, P. Wang, T. Liu, et al., A cell cycle-dependent BRCA1-UHRF1 cascade regulates DNA double-strand break repair pathway choice, Nat. Commun. 7 (2016) 10201, doi:http://dx.doi.org/10.1038/ncomms10201.
[88] V. Boersma, N. Moatti, S. Segura-Bayona, M.H. Peuscher, J. van der Torre, B.A. Wevers, et al., MAD2L2 controls DNA repair at telomeres and DNA breaks by inhibiting 5' end resection, Nature 521 (2015) 537–540, doi:http://dx.doi.org/10.1038/nature14216.
[89] M. Zimmermann, F. Lottersberger, S.B. Buonomo, A. Sfeir, T. de Lange, 53BP1 regulates DSB repair using Rif1 to control 5' end resection, Science 339 (2013) 700–704, doi:http://dx.doi.org/10.1126/science.1231573.
[90] M. Simonetta, I. de Krijger, J. Serrat, N. Moatti, D. Fortunato, L. Hoekman, et al., H4K20me2 distinguishes pre-replicative from post-replicative chromatin to appropriately direct DNA repair pathway choice by 53BP1-RIF1-MAD2L2, Cell Cycle 17 (2018) 124–136, doi:http://dx.doi.org/10.1080/15384101.2017.1404210.
[91] S. Pellegrino, J. Michelena, F. Teloni, R. Imhof, M. Altmeyer, Replication-coupled dilution of H4K20me2 guides 53BP1 to pre-replicative chromatin, Cell Rep. 19 (2017) 1819–1831, doi:http://dx.doi.org/10.1016/j.celrep.2017.05.016.
[92] Y. Li, R.L. Armstrong, R.J. Duronio, D.M. MacAlpine, Methylation of histone H4 lysine 20 by PR-Set7 ensures the integrity of late replicating sequence domains in Drosophila, Nucleic Acids Res. 44 (2016) 7204–7218, doi:http://dx.doi.org/10.1093/nar/gkw333.

[93] H. Yang, J.J. Pesavento, T.W. Starnes, D.E. Cryderman, L.L. Wallrath, N.L. Kelleher, et al., Preferential dimethylation of histone H4 lysine 20 by Suv4-20, J. Biol. Chem. 283 (2008) 12085–12092, doi:http://dx.doi.org/10.1074/jbc.M707974200.
[94] K.D. Bromberg, T.R.H. Mitchell, A.K. Upadhyay, C.G. Jakob, M.A. Jhala, K.M. Comess, et al., The SUV4-20 inhibitor A-196 verifies a role for epigenetics in genomic integrity, Nat. Chem. Biol. 13 (2017) 317–324, doi:http://dx.doi.org/10.1038/nchembio.2282.
[95] S. Wei, C. Li, Z. Yin, J. Wen, H. Meng, L. Xue, et al., Histone methylation in DNA repair and clinical practice: new findings during the past 5-years, J. Cancer 9 (2018) 2072–2081, doi:http://dx.doi.org/10.7150/jca.23427.
[96] M. Herbette, M.G. Mercier, F. Michal, D. Cluet, C. Burny, G. Yvert, et al., The C. elegans SET-2/SET1 histone H3 Lys4 (H3K4) methyltransferase preserves genome stability in the germline, DNA Repair (Amst). 57 (2017) 139–150, doi:http://dx.doi.org/10.1016/j.dnarep.2017.07.007.
[97] Y. Chen, C. Tsai, P. Wang, S. Teng, SMYD3 promotes homologous recombination via regulation of H3K4-mediated gene expression, Sci. Rep. 7 (2017) 3842, doi:http://dx.doi.org/10.1038/s41598-017-03385-6.
[98] K. Arndt, A. Kranz, J. Fohgrub, A. Jolly, A.S. Bledau, M. Di Virgilio, et al., SETD1A protects HSCs from activation-induced functional decline in vivo, Blood 131 (2018) 1311–1324, doi:http://dx.doi.org/10.1182/blood-2017-09-806844.
[99] M.R. Pan, M.C. Hsu, L.T. Chen, W.C. Hung, Orchestration of H3K27 methylation: mechanisms and therapeutic implication, Cell. Mol. Life Sci. 75 (2018) 209–223, doi:http://dx.doi.org/10.1007/s00018-017-2596-8.
[100] K.J. Ferrari, A. Scelfo, S. Jammula, A. Cuomo, I. Barozzi, A. Stützer, et al., Polycomb-dependent H3K27me1 and H3K27me2 regulate active transcription and enhancer fidelity, Mol. Cell 53 (2014) 49–62, doi:http://dx.doi.org/10.1016/j.molcel.2013.10.030.
[101] C. Zhang, Z. Hong, W. Ma, D. Ma, Y. Qian, W. Xie, et al., Drosophila UTX coordinates with p53 to regulate ku80 expression in response to DNA damage, PLoS One 8 (2013) e78652, doi:http://dx.doi.org/10.1371/journal.pone.0078652.
[102] K. Williams, J. Christensen, J. Rappsilber, A.L. Nielsen, J.V. Johansen, K. Helin, The histone lysine demethylase JMJD3/KDM6B is recruited to p53 bound promoters and enhancer elements in a p53 dependent manner, PLoS One 9 (2014) e96545, doi:http://dx.doi.org/10.1371/journal.pone.0096545.
[103] B.H. Rath, I. Waung, K. Camphausen, P.J. Tofilon, Inhibition of the histone H3K27 demethylase UTX enhances tumor cell radiosensitivity, Mol. Cancer Ther. 17 (2018) 1070–1078, doi:http://dx.doi.org/10.1158/1535-7163.MCT-17-1053.
[104] F. Gong, T. Clouaire, M. Aguirrebengoa, G. Legube, K.M. Miller, Histone demethylase KDM5A regulates the ZMYND8-NuRD chromatin remodeler to promote DNA repair, J. Cell Biol. 216 (2017) 1959–1974, doi:http://dx.doi.org/10.1083/jcb.201611135.
[105] F. Gong, L. Chiu, B. Cox, F. Aymard, T. Clouaire, J.W. Leung, et al., Screen identifies bromodomain protein ZMYND8 in chromatin recognition of transcription-associated DNA damage that promotes homologous recombination, Genes Dev. 29 (2015) 197–211, doi:http://dx.doi.org/10.1101/gad.252189.114.
[106] P.L. Sulkowski, S. Oeck, J. Dow, N.G. Economos, L. Mirfakhraie, Y. Liu, et al., Oncometabolites suppress DNA repair by disrupting local chromatin signalling, Nature (2020), doi:http://dx.doi.org/10.1038/s41586-020-2363-0.
[107] M.K. Ayrapetov, O. Gursoy-Yuzugullu, C. Xu, Y. Xu, B.D. Price, DNA double-strand breaks promote methylation of histone H3 on lysine 9 and transient formation of repressive chromatin, Proc. Natl. Acad. Sci. 111 (2014) 9169–9174, doi:http://dx.doi.org/10.1073/pnas.1403565111.
[108] Y. Sun, X. Jiang, Y. Xu, M.K. Ayrapetov, L.A. Moreau, J.R. Whetstine, et al., Histone H3 methylation links DNA damage detection to activation of the tumour suppressor Tip60, Nat. Cell Biol. 11 (2009) 1376–1382, doi:http://dx.doi.org/10.1038/ncb1982.
[109] Y. Sun, X. Jiang, S. Chen, N. Fernandes, B.D. Price, A role for the Tip60 histone acetyltransferase in the acetylation and activation of ATM, Proc. Natl. Acad. Sci. U. S. A. 102 (2005) 13182–13187, doi:http://dx.doi.org/10.1073/pnas.0504211102.
[110] T. Hirota, P. Blakeley, M.N. Sangrithi, S.K. Mahadevaiah, V. Encheva, A.P. Snijders, et al., SETDB1 links the meiotic DNA damage response to sex chromosome silencing in mice, Dev. Cell 47 (2018), doi:http://dx.doi.org/10.1016/j.devcel.2018.10.004.
[111] W. Wu, H. Nishikawa, T. Fukuda, V. Vittal, M. Asano, Y. Miyoshi, et al., Interaction of BARD1 and HP1 is required for BRCA1 retention at sites of DNA damage, Cancer Res. 75 (2015) 1311–1321, doi:http://dx.doi.org/10.1158/0008-5472.CAN-14-2796.
[112] P.H. Dinkelborg, M. Wang, L. Gheorghiu, J.M. Gurski, T.S. Hong, C.H. Benes, et al., A common Chk1-dependent phenotype of DNA double-strand break suppression in two distinct radioresistant cancer types, Breast Cancer Res. Treat. 174 (2019) 605–613, doi:http://dx.doi.org/10.1007/s10549-018-05079-7.
[113] M.K. Ayrapetov, O. Gursoy-Yuzugullu, C. Xu, Y. Xu, B.D. Price, 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 (2014) 9169–9174, doi:http://dx.doi.org/10.1073/pnas.1403565111.
[114] B. Meyer, M.R. Fabbrizi, S. Raj, C.L. Zobel, D.E. Hallahan, G.G. Sharma, Histone H3 lysine 9 acetylation obstructs ATM activation and promotes ionizing radiation sensitivity in normal stem cells, Stem Cell Rep. 7 (2016) 1013–1022, doi:http://dx.doi.org/10.1016/j.stemcr.2016.11.004.
[115] L.C. Young, D.W. McDonald, M.J. Hendzel, Kdm4b histone demethylase is a DNA damage response protein and confers a survival advantage following γ-irradiation, J. Biol. Chem. 288 (2013) 21376–21388, doi:http://dx.doi.org/10.1074/jbc.M113.491514.
[116] J. Stewart-Ornstein, G. Lahav, p53 dynamics in response to DNA damage vary across cell lines and are shaped by efficiency of DNA repair and activity of the kinase ATM, Sci. Signal. 10 (2017), doi:http://dx.doi.org/10.1126/scisignal.aah6671.
[117] H. Zheng, L. Chen, W.J. Pledger, J. Fang, J. Chen, p53 promotes repair of heterochromatin DNA by regulating JMJD2b and SUV39H1 expression, Oncogene 33 (2014) 734–744, doi:http://dx.doi.org/10.1038/onc.2013.6.
[118] Q. Zhao, J. Zhang, R. Chen, L. Wang, B. Li, H. Cheng, et al., Dissecting the precise role of H3K9 methylation in crosstalk with DNA maintenance methylation in mammals, Nat. Commun. 7 (2016) 12464, doi:http://dx.doi.org/10.1038/ncomms12464.
[119] M.D. Stewart, J. Li, J. Wong, Relationship between histone H3 lysine 9 methylation, transcription repression, and heterochromatin protein 1 recruitment, Mol. Cell. Biol. 25 (2005) 2525–2538, doi:http://dx.doi.org/10.1128/MCB.25.7.2525-2538.2005.
[120] H. Liu, M. Galka, E. Mori, X. Liu, Y.-F. Lin, R. Wei, et al., A method for systematic mapping of protein lysine methylation identifies functions for HP1β in DNA damage response, Mol. Cell 50 (2013) 723–735, doi:http://dx.doi.org/10.1016/j.molcel.2013.04.025.
[121] N. Ayoub, A.D. Jeyasekharan, J.A. Bernal, A.R. Venkitaraman, HP1-beta mobilization promotes chromatin changes that initiate the DNA damage response, Nature. 453 (2008) 682–686, doi:http://dx.doi.org/10.1038/nature06875.
[122] W.W. Deng, Q. Hu, Z.R. Liu, Q.H. Chen, W.X. Wang, H.G. Zhang, et al., KDM4B promotes DNA damage response via STAT3 signaling and is a target of CREB in colorectal cancer cells, Mol. Cell. Biochem. 449 (2018) 81–90, doi:http://dx.doi.org/10.1007/s11010-018-3345-5.
[123] A. Mund, T. Schubert, H. Staege, S. Kinkley, K. Reumann, M. Kriegs, et al., SPOC1 modulates DNA repair by regulating key determinants of chromatin compaction and DNA damage response, Nucleic Acids Res. 40 (2012) 11363–11379, doi:http://dx.doi.org/10.1093/nar/gks868.
[124] A. Frohns, F. Frohns, S.C. Naumann, P.G. Layer, M. Löbrich, Inefficient double-strand break repair in murine rod photoreceptors with inverted heterochromatin organization, Curr. Biol. 24 (2014) 1080–1090, doi:http://dx.doi.org/10.1016/j.cub.2014.03.061.
[125] M. Christmann, M.T. Tomicic, W.P. Roos, B. Kaina, Mechanisms of human DNA repair: an update, Toxicology. 193 (2003) 3–34, doi:http://dx.doi.org/10.1016/s0300-483x(03)00287-7.
[126] J.-H. Lee, D.G. Skalnik, CpG-binding protein (CXXC finger protein 1) is a component of the mammalian Set1 histone H3-Lys4 methyltransferase complex, the analogue of the yeast Set1/COMPASS complex, J. Biol. Chem. 280 (2005) 41725–41731, doi:http://dx.doi.org/10.1074/jbc.M508312200.
[127] C.M. Tate, M.L. Fishel, J.L. Holleran, M.J. Egorin, D.G. Skalnik, Embryonic stem cells lacking the epigenetic regulator Cfp1 are hypersensitive to DNA-damaging agents and exhibit decreased Ape1/Ref-1 protein expression and endonuclease activity, DNA Repair (Amst). 8 (2009) 1411–1423, doi:http://dx.doi.org/10.1016/j.dnarep.2009.09.011.
[128] F. Li, G. Mao, D. Tong, J. Huang, L. Gu, W. Yang, et al., The histone mark H3K36me3 regulates human DNA mismatch repair through its interaction with MutSα, Cell. 153 (2013) 590–600, doi:http://dx.doi.org/10.1016/j.cell.2013.03.025.
[129] S. Chaudhuri, J.J. Wyrick, M.J. Smerdon, Histone H3 Lys79 methylation is required for efficient nucleotide excision repair in a silenced locus of Saccharomyces cerevisiae, Nucleic Acids Res. 37 (2009) 1690–1700, doi:http://dx.doi.org/10.1093/nar/gkp003.
[130] Y. Chen, B. Ren, J. Yang, H. Wang, G. Yang, R. Xu, et al., The role of histone methylation in the development of digestive cancers: a potential direction for cancer management, Signal Transduct. Target. Ther. 5 (2020) 143, doi:http://dx.doi.org/10.1038/s41392-020-00252-1.
[131] H. Ueda, Y. Akiyama, S. Shimada, K. Mogushi, M. Serizawa, S. Matsumura, et al., Tumor suppressor functions of DAXX through histone H3.3/H3K9me3 pathway in pancreatic NETs, Endocr. Relat. Cancer 25 (2018) 619–631, doi:http://dx.doi.org/10.1530/ERC-17-0328.
[132] L. Cai, X. Ma, Y. Huang, Y. Zou, X. Chen, Aberrant histone methylation and the effect of Suv39H1 siRNA on gastric carcinoma, Oncol. Rep. 31 (2014) 2593–2600, doi:http://dx.doi.org/10.3892/or.2014.3135.
[133] S. Sunnaghatta Nagaraja, R. Raviraj, I. Selvakumar, D. Dharmalingam, N. Ramadas, D.R. Chellappan, et al., Radiation-induced H3K9 tri-methylation in E-cadherin promoter during lung EMT: and approaches using vanillin, Free Radic. Res. (2020), doi:http://dx.doi.org/10.1080/10715762.2020.1814274.
[134] L.-R. He, M.-Z. Liu, B.-K. Li, H.-L. Rao, Y.-J. Liao, X.-Y. Guan, et al., Prognostic impact of H3K27me3 expression on locoregional progression after chemoradiotherapy in esophageal squamous cell carcinoma, BMC Cancer 9 (2009) 461, doi:http://dx.doi.org/10.1186/1471-2407-9-461.
[135] D. Huang, Y. Qiu, G. Li, C. Liu, L. She, D. Zhang, et al., KDM5B overexpression predicts a poor prognosis in patients with squamous cell carcinoma of the head and neck, J. Cancer 9 (2018) 198–204, doi:http://dx.doi.org/10.7150/jca.22145.
[136] T.P. Xu, W.Y. Wang, P. Ma, Y. Shuai, K. Zhao, Y.F. Wang, et al., Upregulation of the long noncoding RNA FOXD2-AS1 promotes carcinogenesis by epigenetically silencing EphB3 through EZH2 and LSD1, and predicts poor

prognosis in gastric cancer, Oncogene. 37 (2018) 5020–5036, doi:http://dx.doi.org/10.1038/s41388-018-0308-y.
[137] J.H. Kim, A. Sharma, S.S. Dhar, S.H. Lee, B. Gu, C.H. Chan, et al., UTX and MLL4 coordinately regulate transcriptional programs for cell proliferation and invasiveness in breast cancer cells, Cancer Res. 74 (2014) 1705–1717, doi:http://dx.doi.org/10.1158/0008-5472.CAN-13-1896.
[138] M. Gale, J. Sayegh, J. Cao, M. Norcia, P. Gareiss, D. Hoyer, et al., Screen-identified selective inhibitor of lysine demethylase 5A blocks cancer cell growth and drug resistance, Oncotarget. 7 (2016) 39931–39944, doi:http://dx.doi.org/10.18632/oncotarget.9539.
[139] C.-S. Lin, Y.-C. Lin, B.O. Adebayo, A. Wu, J.-H. Chen, Y.-J. Peng, et al., Silencing JARID1B suppresses oncogenicity, stemness and increases radiation sensitivity in human oral carcinoma, Cancer Lett. 368 (2015) 36–45, doi:http://dx.doi.org/10.1016/j.canlet.2015.07.003.
[140] B. Shannan, J. Matschke, H. Chauvistré, F. Vogel, D. Klein, F. Meier, et al., Sequence-dependent cross-resistance of combined radiotherapy plus BRAF inhibition in melanoma, Eur. J. Cancer 109 (2019) 137–153, doi:http://dx.doi.org/10.1016/j.ejca.2018.12.024.
[141] X. Wu, H. Scott, S.V. Carlsson, D.D. Sjoberg, L. Cerundolo, H. Lilja, et al., Increased EZH2 expression in prostate cancer is associated with metastatic recurrence following external beam radiotherapy, Prostate. 79 (2019) 1079–1089, doi:http://dx.doi.org/10.1002/pros.23817.
[142] H. Bur, K.-M. Haapasaari, T. Turpeenniemi-Hujanen, O. Kuittinen, P. Auvinen, K. Marin, et al., Strong KDM4B and KDM4D Expression Associates with Radioresistance and Aggressive Phenotype in Classical Hodgkin Lymphoma, Anticancer Res. 36 (2016) 4677–4683, doi:http://dx.doi.org/10.21873/anticanres.11020.
[143] J. Wei, B. Wang, H. Wang, L. Meng, Q. Zhao, X. Li, et al., Radiation-induced normal tissue damage: oxidative stress and epigenetic mechanisms, Oxid. Med. Cell. Longev. 2019 (2019)3010342, doi:http://dx.doi.org/10.1155/2019/3010342.