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Mi-2/NuRD complex making inroads into DNA-damage response pathway

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Abstract

In eukaryotic cells, packaging of DNA into highly condensed chromatin presents a significant obstacle to DNA-based processes. Cells use two major strategies including histone modifications and ATP-dependent chromatin remodeling to alter chromatin structure that allows protein factors to gain access to nucleosomal DNA. Beyond their well-established role in transcription, histone modifications and several classes of ATP-dependent chromatin-remodeling complex have been functionally linked to efficient DNA repair. Mi-2/nucleosome remodeling and histone deacetylation (NuRD) complex uniquely possess both nucleosome remodeling and histone deacetylation activities, which play a vital role in regulating transcription. However, the role of the Mi-2/NuRD complex in DNA damage response remains largely unexplored until now. Recent findings reveal that metastasis-associated protein 1 (MTA1), an integral component of the Mi-2/NuRD complex, has successfully made inroads into DNA damage response pathway, and thus, links two previously unconnected Mi-2/NuRD complex and DNA damage response research areas. In this review, we will summarize recent progress concerning the functions of histone modifications and chromatin remodeling in DNA repair, and discuss new role of Mi-2/NuRD complex in DNA damage response.

Keywords

Chromatin-remodeling complex; Histone modification; Acetylation and deacetylation; DNA repair; Mi-2/NuRD complex; MTA1

Eukaryotic genome is packaged into chromatin, which generally reduce accessibility for enzymes that mediate DNA-based cellular processes such as transcription, DNA replication, or DNA damage repair [1, 2]. To overcome these regulatory barriers, eukaryotic cells use two major strategies to modify chromatin structures. The first is by post-translational modifications of histones and second by ATP-dependent nucleosome remodeling-both implicated in transcriptional regulation[2–7]. By analogy to transcription, DNA damage is detected and repaired in the context of chromatin. Therefore, in order for damaged DNA to be repaired efficiently, there must be restructuring of the chromatin to facilitate the accessibility of repair machinery to the site of DNA lesion. As expected, recent studies reveal that histone modifications[8–10] and several classes of ATP-dependent chromatin-remodeling complexes[11–14] also function in ensuring efficient DNA repair.

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Role of histone acetylation/deacetylation in DNA repair

The core histone tails are susceptible to a variety of covalent modifications, including acetylation, methylation, phosphorylation, and ubiquitination[15]. Due to its tight association with transcriptional regulation, histone acetylation is probably one of the best studied modifications. In eukaryotes, the histones are acetylated and deacetylated on lysine residues in the N-terminal tail and on the surface of the nucleosome core, which regulate chromatin accessibility. Typically, these reactions are catalyzed by enzymes with histone acetyltransferase (HAT) or histone deacetylase (HDAC) activity[16]. Like its role in transcription[7], histone acetylation might modulate the accessibility of damaged-DNA site to DNA-repair machinery or provide appropriate binding surfaces for repair proteins[16, 17]. Now it becomes increasingly clear that histone acetylation functions in specific DNA-repair pathways. For example, it was found that deletion of the N-terminal tail of or mutation of the acetylatable lysines (Lys 5, Lys 8, Lys 12, and Lys 16) of histone H4 renders cells hypersensitive to DNA double-strand break (DSB)-damaging agents [8, 18]. Importantly, reintroduction of a single acetylatable lysine anywhere in the mutant histone H4 tail restores wild-type levels of resistance to DSB damage[8], indicating that H4 acetylation plays an important role in DNA repair. In line with these findings, acetylation of histone H4 by the mammalian Trrap (transformation/transcription domain-associated protein)/Tip60 (Tat-interactive protein 60 kDa) HAT complex is required for recruitment/loading of repair proteins to DSBs[19]. In this context, Trrap depletion impairs both DNA-damage-induced histone H4 hyperacetylation and accumulation of repair molecules at DSBs. This in-turns, result in defective homologous recombination (HR) repair, albeit with the presence of a functional ataxia telangiectasia mutant (ATM)-dependent DNA-damage signaling cascade[19]. Importantly, the impaired loading of repair proteins and the defect in DNA repair in Trrap-deficient cells can be counteracted by chromatin relaxation, indicating that the observed DNA-repair defect in the absence of Trrap was due to impeded chromatin accessibility at the site of DNA breaks [19]. Similarly, ectopic expression of mutated Tip60 lacking histone acetylase activity results in cells with defective DSB repair[20].

In *S. cerevisiae*, acetylation of histone H4 by the catalytic subunit ESA1 (the yeast homolog of Tip60) of the NuA4 (nuclesome acetyltransferase of H4) HAT complex is also required for DSB repair [8]. This was further supported by the finding that mutation in ESA1 results in increased cellular sensitivity to DSB-inducing agents and a defect in non-homologous end joining (NHEJ)[8]. In addition, mutation of Yng2, another component of the yeast NuA4 HAT complex, results in critical defect for genome-wide nucleosomal histone H4 acetylation, and hypersensitivity to and inefficient repair of DNA damage caused by genotoxic agents that induce replication fork stalling [21]. During HR repair in yeast, the HAT Gnc5 is specifically recruited to DSB sites, where it contributes to an increased H3 and H4 histone acetylation at the site of break-flanking[22]. In addition, mutations in either specific lysine residues in the histone H3 tail or the yeast histone acetyltransferase Hat1p influences the HR repair of DSBs through Asf1p-dependent chromatin assembly, resulting in hypersensitivity to DSB-inducing agents [23].

Interestingly, histone deacetylation activities have also been linked to DSB repair [9]. For example, it was shown that Sir2p, an NAD-dependent HDAC, and its interacting partners, Sir3p and Sir4p, influence NHEJ [24–26]. Furthermore, these factors re-localize from telomeres to the site of DNA DSBs, and cells lacking these factors exhibit a defect in NHEJ[24–26]. A recent study further demonstrates that the Sin3p/Rpd3p HDAC complex is required for an efficient repair by NHEJ in *S. cerevisiae* [10]. In this context, lysine 16 of histone H4 (H4K16) is deacetylated in the vicinity of chromosomal DSBs, and this deacetylation requires the HDAC Sin3-Rpd3. Furthermore, Sin3 or Rpd3 mutants are defective in NHEJ and are susceptible to DSBs [10]. In line with this finding, studies from the

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same group also showed that acetylation of histone H3 on lysine 9 (H3K9Ac) and lysine 56 (H3K56Ac) is reduced in response to DNA damage in human cells identified by a large-scale screen for DNA-damage-responsive histone modifications, although the precise functions of H3K9Ac and H3K56Ac in the DNA damage response remains to be defined [27]. Recently, H3K56Ac has been reported to have a role in DNA repair in yeast [28]. Mutation of K56 in histone H3 display hypersensitivity to DNA damaging agents, specifically those that induce damage during S-phase[29, 30]. H3K56Ac is predicted to result in an opening of the nucleosome at the DNA entry/exit points, which could facilitate recruitment of repair factors[31]. Alternatively, or in addition, H3K56ac could serve as a recruitment site for bromodomain-containing protein involved in repair process[31]. Interestingly, bromodomains are conserved protein sequence motifs that are present in the subunits of the RSC (remodels the structure of chromatin), SWI/SNF (switching/sucrose non-fermenting), and SWR1 (SWT2-related ATPase 1) chromatin-remodeling complexes. In support of this hypothesis, a very recent study showed that acetylation of H3K56 does not directly affect the compaction of chromatin but has modest effects on remodeling by SWI/SNF and RSC complexes [32].

Interestingly, it was suggested that after ultraviolet (UV) irradiation all histones display a rapid hyperacetylation phase followed by a hypoacetylated state, although the specific histone marks that changed were unidentified [33]. It is possible that acetylation is required initially to relax the chromatin, allowing access of repair proteins, and the subsequent deacetylation may serve to locally stabilize the chromatin for rejoining of the DNA ends [6, 10]. Another possibility is that the HDAC is first recruited to create a hypoacetylated region to allow efficient stabilization and juxtaposition of the two broken ends. Once the repair process is completed the HAT is recruited to help re-establish the correct histone code to allow efficient DNA repair [6, 10]. Thus, these two activities might even be recruited to the site of damage as parts of one complex[10]. Consistent with this hypothesis, it was shown that localized acetylation of histones H3 and H4 is triggered by HR through the histone acetyltransferases Gcn5 and ESA1 and subsequently removed by the histone deacetylases Rpd3, Sir2, and Hst1 [22].

Role of ATP-dependent nucleosome-remodeling complexes in DNA repair

In addition to histone modifications, chromatin structure can also be altered by ATP-dependent chromatin-remodeling complexes that utilize energy from ATP hydrolysis to remove or reposition nucleosomes, thereby altering chromatin structure and influencing the accessibility of DNA to other factors [4, 12, 13, 34–37]. Based on the different ATPase subunits, the remodeling complexes could be divided into three groups [15, 38]. The first group uses the switch 2/sucrose non-fermenting 2 (SWI2/SNF2) or a close relative as the ATPase and includes yeast/human SWI/SNF complex, yeast RSC, and the *drosophila* Brahama complex[15]. The INO80 (inositol auxotroph 80) complex is the most recent addition to the SWI/SNF family of chromatin remodelers[11]. The INO80 complex includes INO80 and SWR1 in *S. cerevisiae*; INO80, SNF2-related CREB-binding protein (CBP) activator protein (SRCAP), and p400 in mammal; and INO80 and p400 in *Drosophila melanogaster*[11]. The second group uses imitation switch (ISWI) or a close relative as the ATPase and includes NURF (nuclesome remodeling factor), CHRAC (chromatin-accessibility complex), and ACF (ATP-utilizing chromatin assembly and remodeling factor) from *Drosophila*[15]. The third group uses Mi-2 as the ATPase and includes human nuclesome remodeling and histone deacetylase (NuRD)[39–41] and its counterpart in *xenopus*, the Mi-2 complex[42]. Recently, at least four distinct ATP-dependent chromatin remodeling complexes, including SWI/SNF, INO80, SWR1, and RSC complexes, have been directly implicated in DNA repair in yeast and mammalian cells [13, 43–46].

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Among them, RSC seems uniquely suited for a role in early chromatin remodeling at the DSB, because it is rapidly recruited to the DSB and functions in both NHEJ and HR [47–49]. RSC participates in an early step of DSB repair by preparing the binding site for the Mre 11 and Ku complex[49], as depletion of the ATPase subunit Sth1 or Rsc2 severely reduces chromatin remodeling and loading of Mre11 and Ku at the sites of DSBs. In addition, RSC also recruits Tel 1 and Mec 1 (the yeast ATR and ATM homolog, respectively) to the breaks site, and is necessary to ensure full levels of H2AX phosphorylation[50]. Consistent with these results, it was shown that Rsc2 is needed for efficient activation of the Rad53-dependent checkpoint, Cohesin's association with the break site, and the DNA-damage-induced changes in nucleosome structure surrounding the DSB site[50]. Furthermore, the Rsc1p subunit of RSC directs nucleosome sliding immediately after DSB creation and is required for efficient induction of γ-H2A and strand resection during repair by HR [51]. These findings suggest that the RSC complex participates in remodeling and in increasing the ability of MRN to bind and medicate resection of DNA ends [43].

Accessibility within chromatin is an important factor in the prompt removal of UV-induced DNA damage by nucleotide excision repair (NER). This repair pathway is used for the removal of the UV-induced cyclobutane pyrimidine dimer (CPD) and pyrimidine (6–4) pyrimidone photoproducts. Chromatin remodeling by the SWI/SNF complex has been shown to play an important modulating role in NER *in vitro* and *in vivo* [52]. It was shown that Brg1, the ATPase subunit of SWI/SNF, facilitates different stages of NER by initially modulating UV-induced chromatin relaxation and stabilizing xeroderma pigmentosum group C (XPC) at the damage sites. This subsequently stimulates the recruitment of xeroderma pigmentosum group G (XPG) and proliferating cell nuclear antigen (PCNA) to successfully culminate the repair [52]. In support of this observation, it was reported that the SWI/SNF-deficient human carcinoma cell line SW13 cells are sensitive to UV radiation. In contrast, SW13 cells with ectopic Brg1 expression regain active SWI/SNF and become significantly more resistance to UV radiation, suggesting that SWI/SNF protects cells against deleterious consequences of UV-induced DNA damage [53]. In addition, human SWI/SNF core subunit SNF5 (hSNF5) also associates with UV damage recognition factor XPC at the damage site in response to UV irradiation and promotes NER by influencing the recruitment of ATM kinase to the damage site and activation of ATM by phosphorylation[54]. Consequently, SNF5 deficiency results in a defect in H2AX and breast cancer type 1 susceptibility protein (BRCA1) phosphorylation at the damage site[54] and increased sensitivity to geneotoxic stress, suggesting a role of SNF5 in the DNA damage response[55]. A study in yeast by Gong and colleagues demonstrated enhanced interaction between the Rad4 (the yeast homologue of XPC) and two subunits of SWI/SNF complex, SNF5 and SNF6, after UV irradiation[53]. In *S. cerevisiae*, SWI/SNF complex enhances the repair of UV-induced CPDs in chromatin by photolyase [56] and stimulates the excision of chemical adducts within the core nucleosome[57]. In addition to its role in stimulating NER of damaged chromatin, it was found that the mammalian SWI/SNF complex is also recruited to the sites of DSBs and facilitates DSB repair by promoting γ-H2AX induction at DSB-surrounding chromatin following ionizing radiation (IR) treatment[14, 47]. The inactivation of SWI/SNF subunits leads to deficient H2AX phosphorylation in the presence of normal ATM, ATM and rad3-related protein (ATR), and DNA-dependent protein kinase (DNA-PK) activation and inefficient DSB repair [14].

Similarly, the INO80 complex is recruited to a HO endonuclease-induced DSB through direct interaction of its Arp4 or Nhp10 subunit with γ-H2AX, and the loss of γ-H2AX results in reduced INO80 recruitment to the DSB [2, 3, 58]. Notably, the yeast strains lacking a functional INO80 complex are hypersensitive to DSB-inducing genotoxic agents [2, 3, 5]. A recent study suggests that RNA interference-mediated knockdown of INO80 increased cellular sensitivity toward UV-induced DNA damage as determined by survival assays[59].

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Functional assays revealed that INO80 is essential for HR-based DNA repair[59]. It was shown that Ies4 subunit of the INO80 complex is phosphorylated by the Mec1/Tel1 (ATM/ATR in mammals) kinase in response to DNA damage, and mutation of phosphorylation sites of les4 influences DNA damage checkpoint pathways [60]. The INO80 Arp4 subunit that interacts directly with γ-H2AX is also present in the histone exchange complex SWR1[61]. Depletion of the SWR1 subunit also renders cells hypersensitive to DNA damaging agents[61, 62], and this complex also catalyzes chromatin structure alternations at DSBs through exchange of γ-H2A and H2AZ [63, 64]. Taken together, it is becoming increasing clear that histone acetylation/deactylation and chromatin remodeling facilitate DNA repair beyond their well-documented role in transcription, presumably by opening or loosening compact nucleosomal structure close to sites of damage.

Mi-2/NuRD complex uniquely possesses both nucleosome remodeling and HDAC activities

The Mi-2/NuRD complex is a multi-subunit complex that consists of a SNF2-related chromatin remodeling ATPase (Mi-2), a member of the MBD family of methyl CpG binding domain proteins (MBD3), histone deacetylases (HDAC1 and HDAC2), a histone binding protein (RbAp46/p48), a protein of unknown function (known as p66), an interesting subunit encoded by one of three genes (MTA1, MTA2, or MTA3) in mammals [65–68]. The composition of this complex is highly conserved from *xenopus* to human. This complex, Mi-2/NuRD, is the only known protein entity that uniquely possesses both nucleosome remodeling and histone deacetylase activities[15, 67]. It has been shown to play a central role in transcriptional regulation of a number of target genes in vertebrates, invertebrates and fungi [15, 40, 66, 67, 69]. Although the complex is often lined with transcriptional repression associated with the HDAC activity and the intrinsic nucleosome remodeling activity of Mi-2[67], the function of NuRD complex in transcriptional activation has been suggested[70]. For example, it was found that Mi-2α, previously studied as a subunit in the NuRD co-repressor complex, enhanced c-Myb-dependent reporter activation[70]. The rationale for the unexpected co-activator function seems to lie in a dual function of Mi-2α, by which this factor is able to repress transcription in a helicase-dependent and activate in a helicase-independent fashion, as revealed by Gal4-tethering experiments[70]. In addition, NuRD complex also plays a role in transcriptional termination[71], centrosome maintenance[72,73], tumorigenesis, and tumor progression[74,75]. Given that ATP-dependent chromatin remodeling has mechanistically similar role in transcription and DNA damage repair by disrupting chromatin to give regulatory and repair factors direct access to DNA, it is reasonably postulated that the Mi-2/NuRD complex, like other ATP-dependent chromatin-remodeling complexes[11, 12, 34, 36], might be involved in DNA damage repair, beyond its well-established role in transcription [67].

MTA1, an integral component of Mi-2/NuRD complex, is a multifunctional DNA damage responsive protein

One integral subunit of the NuRD complex is the metastasis-associated protein 1 (MTA1), which was originally identified by differential cDNA library screening using the highly metastatic and nonmetastatic rat mammary adenocarcinoma cell lines[76]. Subsequent studies demonstrate that MTA1 is up-regulated in a wide range of human cancers and plays an important role in tumorigenesis, tumor invasion and metastasis [74, 75]. As a dual-function coregulator by modulating the accessibility of DNA to transcription factors[77], MTA1 functions not only as a transcriptional repressor of estrogen receptor-α[78], BRCA1[79], Six3[80], and p21*WAF1*[81] genes, but also as a transcriptional activator *via* interacting with RNA polymerase II on the breast cancer-amplified sequence 3 (BCAS3)[82] and paired box gene 5

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(Pax5) [83] promoters. The co-repressor *versus* co-activator activity of MTA1 might be influenced by its binding partners on the promoter region of various genes. In addition to deacetylation of histone, MTA1/2-HDAC complex has been shown to interact with and deacetylate non-histone proteins, including p53, hypoxia-inducible factor-1α, and estrogen receptor-α[84]. Interestingly, MTA1 also undergoes autoacetylation[82]. In this context, MTA1 is acetylated at lysine 626 by histone acetyltransferase p300, which might contribute to its co-activator activity on BCAS3 transcription[82]. However, new functions and related signaling transduction pathways of MTA1 remain to be further explored. Since it is becoming increasingly clear that chromatin structure has an impact on the DNA damage response and is modulated in response to DNA damage [85], it is therefore not surprising that our recent findings have linked the chromatin modifier MTA1 to DNA-damage response pathway, in addition to its paramount role in cancer and coregulator biology.

Initial evidence for a role of MTA1 protein in DNA damage response pathway came from experiments showing that MTA1 is stabilized in response to IR[86]. Mechanistically, MTA1 is targeted by the E3 ubiquitin ligase constitutive photomorphogenesis 1 (COP1) for degradation *via* the ubiquitin-proteasome pathway[86]. In response to DNA damage, ATM kinase phosphorylates COP1 on Serine 387 and promotes its auto-degradation [87], which might contribute to the increase in MTA1 stability following DNA damage by dampening the ability of COP1 to negatively regulate MTA1. One of the hallmarks of defective DNA repair is increased radiation sensitivity. We found that knockout of MTA1 ($MTA1^{-/-}$) in mouse embryonic fibroblasts (MEFs) resulted in increased cellular sensitivity to IR that induces DSBs and decreased clonogenic survival, suggesting that MTA1 is important for cell survival after DNA damage [86]. We further demonstrated that MTA1 is involved in DSB repair. Neutral comet assay that specifically measures DNA DSBs [14, 88] showed that $MTA1^{-/-}$ MEFs exhibit a decreased repair efficiency and an increased level of damaged DNA as compared with its wild-type controls after IR treatment. Given the fact that $MTA1^{-/-}$ MEFs still contain MTA2 and MTA3 [86, 88], we concluded that MTA1 is required for efficient DSB repair.

One of the early events in mammals in response to the induction of DNA damage is the rapid phosphorylation of histone H2AX on Serine 139 by the phosphatidylinositol-3 kinase-like family of kinases at the DSB site [89–91]. It is believed that ATM is the major kinase responsible for phosphorylating H2AX in response to DSBs[92], where ATR is also required for UV-induced damage and DNA damage occurring at stalled replication forks[93]. Phosphorylated H2AX (referred to as γ-H2AX) in mammalian cells accumulates upon damage in the chromatin surrounding DSBs (known as nuclear foci), and recruits a multitude of other factors implicated in DSB repair to region of damaged chromatin in order to mend the damage[14, 90, 91, 94–96]. Thus, the absence of γ-H2AX foci correlates with impaired formation of repair foci at sites of damage [2, 90]. Several studies in mammalian cells implicate H2AX in both NHEJ and HR repair pathways [92, 93, 97], and mouse embryonic stem cells deficient for H2AX were shown to be sensitive to IR-induced DSBs [94, 98]. Interestingly, we found that knockout of MTA1 decreased the induction of γ-H2AX and compromised the γ-H2AX foci formation in response to IR[86]. Importantly, the observed defect in γ-H2AX induction in the MTA1-knockout cells was efficiently restored by reintroduction of MTA1 in these MTA1-deficient cells[86], suggesting that MTA1 is critical for the induction of γ-H2AX and the formation of γ-H2AX foci in response to IR-induced DSBs. Therefore, it is tempting to propose that MTA1-containing Mi-2/NuRD complex, like the SWI/SNF complexes[14], can function upstream of γ-H2AX, whereas the INO80 complex rather contributes to the downstream repair events[3]. The INO80 complex, albeit it interacts with γ-H2AX, is not required for the induction of γ-H2AX following DNA damage[3], whereas mammalian SWI/SNF and Mi-2/NuRD complexes are critical for the optimal induction of γ-H2AX[14, 86]. Thus, different members of the ATP-dependent chromatin

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remodeling complex family may adopt distinct mechanisms for facilitating DSB repair. Given the crucial role for γ-H2AX in chromosomal DSB repair and cell survival after DNA damage, these results suggest that MTA1 facilitates DSB repair and hence increase the resistance to DNA damage, at least in part, by promoting γ-H2AX induction. Since γ-H2AX induction is an early event in DSB repair and has been implicated in both NHEJ and HR pathways [99, 100], MTA1 might be required for the processing of newly broken DNA ends in a nucleosomal context to facilitate HR or NHEJ. Our findings have raised a number of interesting questions to be addressed. For example, whether MTA1 directly interacts with γ-H2AX, and how MTA1 affects γ-H2AX induction in response to DNA damage would be the subject of continued studies. For example, whether MTA1 affects the expression of the kinases, ATM, ATR, DNA-PK, which are all responsible for the phosphorylation of H2AX, or directly acts on the chromatin to facilitate H2AX phosphorylation. Alternations of the structure of the Mi-2/NuRD remodeling could directly affect the accessibility of H2AX at the sites of DSBs. Thus, the Mi-2/NuRD complex might facilitate H2AX phosphorylation by influencing the higher order chromatin structure in such a way as to increase the accessibility of the H2AX-containing nucleosomes.

As mentioned above, recent studies indicate that γ-H2AX is required for the recruitment of chromatin-remodeling complex to the sites of DNA damage. In line with this notion, γ-H2AX in yeast is required for the recruitment of the NuA4 HAT complex to a region proximal to a DSB induced by HO endonuclease [58]. The recruitment of this HAT complex to γ-H2AX is mediated by Arp4 and leads to acetylation of chromatin surrounding the break site, thereby facilitating efficient repair of DNA damage [58]. Arp4 is also a subunit of the INO80 chromatin remodeling complex, which is also recruited to a DSB by a specific interaction with γ-H2AX [2, 3]. In support of this notion, loss of γ-H2AX results in reduced INO80 recruitment to the DSBs [2, 3], which in turn is required for efficient processing of the DSB into single-stranded DNA[2]. Similarly, phosphorylation of H2AX results in the recruitment of the SWR1 chromatin-remodeling complex [58]. Thus, whether γ-H2AX facilitates the recruitment of MTA1-containing Mi-2/NuRD complex to the damaged chromatin after DNA damage remains to be further investigated. Although MTA1 facilitating DSB repair might be through promoting the γ-H2AX induction, we cannot formally exclude the possibility that MTA1 also contributes to DSB repair by regulating the expression of yet unidentified DSB repair proteins.

The p53 protein is a critical component of the DNA damage response that plays numerous roles in a variety of DNA repair pathways, including DSB, single-strand break, base excision repair, and mismatch repair[101, 102]. To further investigate the potential mechanism for the role of MTA1 protein in DSB repair, we found that MTA1 interjects into the p53-dependent DNA repair[88]. In this context, MTA1 is required for the stabilization of p53 protein by inhibiting its ubiquitination mediated by E3 ubiquitin ligases [88]. As a result, MTA1 regulates the p53-dependent transcription of p53R2, a direct p53 target gene for supplying nucleotides to repair damaged DNA [88, 103]. The ability of p53R2 to supply nucleotides for repairing DNA damage requires the presence of a functional p53 protein[103], and inactivation of p53R2 impairs DNA repair and sensitizes several types of cancer cells to DNA-damaging anticancer agents or to ionizing radiation (IR)[103–105]. We found that knockout of MTA1 impairs p53-dependent p53R2 transcription and compromises DNA repair. Interestingly, these events could be reversed by MTA1 reintroduction in the $MTA1^{-/-}$ cells[88]. Given the fact that there was no compensatory effect of MTA1 depletion in MEFs on the levels of MTA2[88], which as a part of the NuRD complex has been previously shown to deacetylate p53 and inhibits p53-dependent transcription of genes important in cell growth and apoptosis [106], these findings suggest that MTA1 interjects into the p53-dependent DNA repair [88] (Fig. 1).

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Following this observation, we further discovered a p53-independent role of MTA1 in DNA damage response. $p21^{WAF1}$ represents one of the best characterized downstream targets of p53[107, 108], and inhibits various PCNA-dependent DNA repair processes by binding to PCNA and interfering with PCNA-dependent DNA polymerase activity[109–112]. Our recent findings reveal that MTA1 is a p53-independent transcriptional co-repressor of $p21^{WAF1}$ by recruitment of MTA1/HDAC2 complexes onto $p21^{WAF1}$ promoter[81]. As a result, MTA1 depletion, in spite of its effect on p53 down-regulation, superinduces $p21^{WAF1}$, increases $p21^{WAF1}$ binding to PCNA, and decreases the nuclear accumulation of PCNA in response to IR-induced damage[81, 88]. Consequently, MTA1 expression in p53-null cells results in increased induction of γ-H2AX foci and DSBs repair, and decreased DNA damage sensitivity following IR treatment. These findings uncover the existence of an additional p53-independent role of MTA1 in DNA damage response, at least in part, by modulating $p21^{WAF1}$-PCNA pathway[81](Fig.1).

Several lines of evidence have implicated the SWI/SNF chromatin remodeling complex in efficient repair of UV-induced DNA damage [52–54, 56, 113]. In addition to its role in the repair of DSBs caused by IR, recent studies reveal that MTA1 also participates in UV-induced DNA damage checkpoint pathway. It was shown in an earlier study that the components of Mi-2/NuRD complex, including MTA1, MTA2, HDAC1, HDAC2, and Mi-2, could be detected in the immunoprecipitates of ATR[114], one of key regulators of the checkpoint pathways in the mammalian DNA damage response[115]. These results suggest that there may be a linkage between the role of ATR in mediating checkpoints induced by DNA damage and chromatin modulation *via* remodeling and deacetylation[114]. It is well accepted that ATM is primarily activated by DSB-inducing agents including IR, while ATR is activated by stalled replication forks and agents that produce bulky adducts, such as UV irradiation[115, 116]. Furthermore, a recent study showed that UV irradiation induces the protein expression of Mi-2, a core subunit of the Mi-2/NuRD complex[39–42], by regulating protein translation and stability [117]. Based on these findings, we hypothesized that Mi-2/NuRD complex may implicate in the UV-induced DNA damage response in mammalian cells and contribute to the regulation of DNA damage checkpoints. In support of this hypothesis, we found that MTA1 is required for activation of ATR following UV irradiation, as depletion of MTA1 severely impaired ATR-dependent phosphorylation of checkpoint kinase 1 (Chk1) and H2AX[118]. These findings further support the notion that MTA1 might act as an upstream regulator of γ-H2AX in response to IR- or UV-induced DNA damage. As a result, depletion of MTA1 results in the abrogation of G2-M checkpoint and increased cellular sensitivity to UV-induced DNA damage[118]. The molecular mechanism for the requirement of MTA1 in the ATR-mediated checkpoint activation is currently being investigated in our lab. One possibility is that MTA1 as a chromatin modifier could alter chromatin structure in an unknown way in response to DNA damage, resulting in increased accessibility of damaged DNA to repair factors. Taken together, these findings suggest that MTA1 also plays a role in UV-induced ATR-mediated DNA damage checkpoint pathway (Fig.1).

Conclusion and perspective

In summary, it is becoming increasingly clear that, like other chromatin-remodeling complexes, Mi-2/NuRD complex is also implicated in DNA damage repair, emphasizing the evolutionally conserved functions of this family of chromatin-remodeling complexes in DNA repair. In the context, we found that MTA1, an integral component of Mi-2/NuRD complex, is a multifunctional DNA damage responsive protein and involved in multiple DNA damage pathways (Fig. 1). Based on lessons learned from transcription, the Mi-2/NuRD remodeling complex might be used to generate nucleosome-free regions around the DNA damage sites in order to facilitate the access of large DNA repair machinery or to

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create specific chromatin structure suitable for DNA repair[3]. Studies addressing the molecular mechanism by which it does so are in their infancy and many more questions remain to be addressed. Such studies may reveal where and how Mi-2/NuRD complex induces changes in chromatin near sites of damage, and how this influences DNA repair. Importantly, DNA damage responsive proteins play key roles in tumorigenesis, and their activities, in part, determine the outcome of cancer radiotherapy and chemotherapy that function by generating DNA damage[119]. DNA repair provides as a common mechanism for cancer-therapy resistance. Given the fact that MTA1 is widely up-regulated in human cancers and facilitates the repair of the damaged DNA, it is speculated that drugs or inhibitors targeting MTA1 may effectively sensitize tumor cells to radiotherapy and DNA-damaging chemotherapies.

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Abbreviations

ATM	ataxia telangiectasia mutant
ATR	ATM and Rad-3 related
DSB	double-strand break
HAT	histone acetyltransferase
HDAC	histone deacetylase
HR	homologous recombination
INO80	inositol auxotroph 80
IR	ionizing radiation
MEF	mouse embryonic fibroblast
MTA1	metastasis-associated protein 1
NER	nucleotide excision repair
NHEJ	non-homologous end joining
NuA4	nucleosome acetyltransferase of H4
NuRD	nucleosome remodeling and histone deacetylase
RSC	remodels the structure of chromatin
SWI/SNF	switching/sucrose non-fermenting
SWR1	SWI2-realted ATPase 1
UV	ultraviolet

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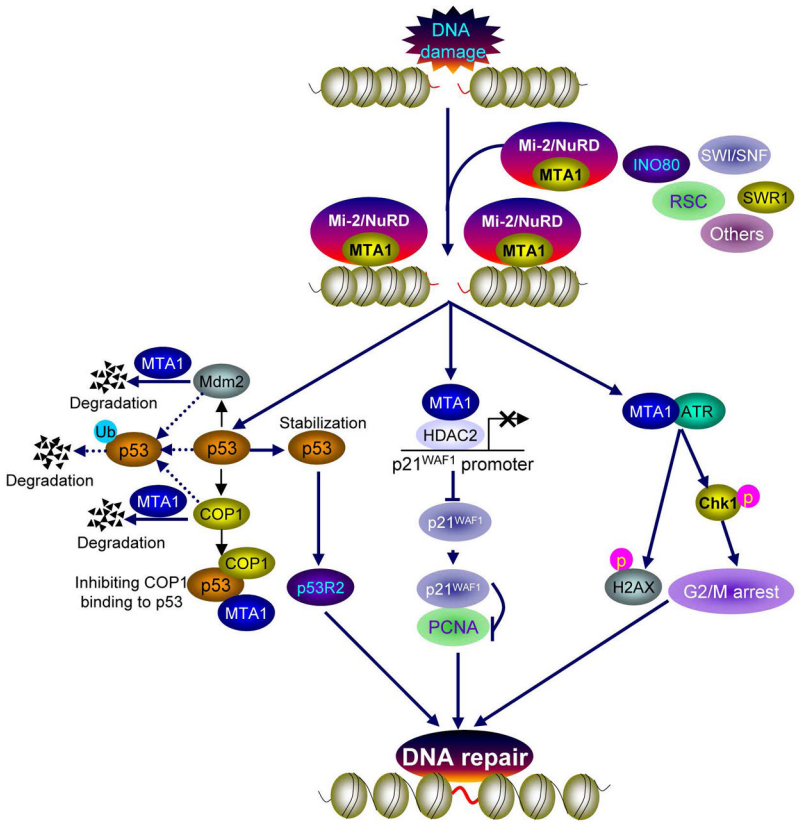

Figure 1. Summary of recently discovered functions of MTA1 in DNA damage response

In response to DNA damage, the Mi-2/NuRD complex, like other ATP-dependent chromatin remodeling complexes (such as INO80, SWI/SNF, RSC, and SWR1), might be recruited to the site of damaged DNA, and exerts its function in DNA repair by multiple different mechanisms. It was shown that MTA1, an integral component of the Mi-2/NuRD complex, is a multiple functional DNA damage responsive protein. MTA1 regulates p53-dependent and –independent DNA repair processes following IR treatment by modulating the p53-p53R2 and $p21^{WAF1}$-PCNA pathway, respectively. In this context, MTA1 controls p53 stability through inhibiting the E3 ubiquitin ligases Mdm2- and COP1-mediated ubiquitination by destabilizing of Mdm2 and COP1 and/or by competing with COP1 to bind to p53, thereby regulating the p53-dependent transcription of p53R2, a direct p53 target gene for supplying nucleotides to repair damaged DNA (left panel). In addition, MTA1 transcriptionally suppresses $p21^{WAF1}$ expression by recruitment of MTA1/HDAC2 complex onto $p21^{WAF1}$ promoter, and inhibits $p21^{WAF1}$ binding to PCNA, thereby facilitates PCNA-dependent DNA repair. In addition, MTA1 is required for ATR-mediated DNA damage checkpoint function in response to UV irradiation. In this case, MTA1 interacts with ATR and is required for the ATR-mediated Chk1 activation and γ-H2AX induction following UV irradiation. Consequently, MTA1 deficiency results in a defective G_2/M DNA damage checkpoint and increased cellular sensitivity to UV irradiation.