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MTA family of proteins in DNA damage response: mechanistic insights and potential applications

Da-Qiang Li,

Fudan University Shanghai Cancer Center and Institutes of Biomedical Sciences, Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China

Yinlong Yang, and

Department of Oncology and Breast Surgery, Shanghai Medical College, Fudan University, Shanghai 200032, China

Rakesh Kumar

Department of Biochemistry and Molecular Medicine, George Washington University, Washington, DC 20037, USA

Abstract

The DNA damage, most notably DNA double-strand breaks, poses a serious threat to the stability of mammalian genome. Maintenance of genomic integrity is largely dependent on an efficient, accurate, and timely DNA damage response in the context of chromatin. Consequently, dysregulation of the DNA damage response machinery is fundamentally linked to the genomic instability and a likely predisposition to cancer. In turn, aberrant activation of DNA damage response pathways in human cancers enables tumor cells to survive DNA damages, thus, leading to the development of resistance of tumor cells to DNA damaging radio- and chemotherapies. A substantial body of experimental evidence has established that ATP-dependent chromatin remodeling and histone modifications play a central role in the DNA damage response. As a component of the nucleosome remodeling and histone deacetylase (NuRD) complex that couples both ATP-dependent chromatin remodeling and histone deacetylase activities, the metastasis-associated protein (MTA) family proteins have been recently shown to participate in the DNA damage response beyond its well-established roles in gene transcription. In this thematic review, we will focus on our current understandings of the role of the MTA family proteins in the DNA damage response and their potential implications in DNA damaging anticancer therapy.

Keywords

Chromatin remodeling; DNA damage response; Double-strand break repair; Histone modification; Metastasis-associated protein; NuRD complex; Therapeutic resistance

1 Introduction

The metastasis-associated proteins (MTAs) consist of a family of gene products encoded by three distinct transcripts, namely MTA1, MTA2, and MTA3 [1,2]. The MTA proteins contain three conserved structural domains, namely, BAH (bromo-adjacent homology) domain, ELM2 (EGL-27 and MTA1 homology 2) domain, and SANT (SWI3, ADA2, N-CoR, and TFIIIB) domain [1]. Accumulating structural and biochemical evidence suggests that the BAH domain plays diverse and versatile roles in chromatin biology, including protein-protein interactions, recognition of histone tails, nucleosome binding, and chromatin assembly [3-5]. Although its function has not been well characterized to date, the ELM2 domain is usually found in a number of transcription cofactors, and thus, highlighting its potential role in regulating gene transcription [6-8]. The SANT domain has been widely appreciated as a DNA- and histone tail-binding module, which is present in multiple chromatin remodeling enzymes, and essential for their enzymatic activities [9-12]. Collectively, the presence of multiple important structural domains indicates potential functions of the MTA family proteins in regulating DNA-based biological processes, such as gene transcription and DNA damage repair. Although the role of the MTA family proteins in gene transcription has been well documented [1,2, 13-15], emerging unexpected observations have recently implicated the MTA family proteins in DNA damage response (DDR) [16-22]. Here, we will summarize recent advances in our understandings of the contribution of the MTA family proteins to the DNA damage signaling and repair, and their potential implications in DNA damage-based anticancer therapy.

2 DDR in the context of chromatin

Cellular DNA is constantly being damaged by various exogenous and endogenous genotoxic agents that pose a significant threat to the stability of mammalian genome [23]. In particular, the DNA double-strand breaks (DSBs) is one of the most toxic types of DNA damage, which can result in chromosomal aberrations and gene mutations [24, 25]. Accordingly, the inability of cells to efficiently and precisely repair the damaged DNA can lead to a high level of the genomic instability, one of the recognized hallmarks of human cancer [26-30].

To maintain the integrity of the genome which is challenged by DNA damage, cells have developed versatile complex mechanisms, collectively known as the DDR, to detect, signal and repair the damaged DNA lesions in a coordinated manner [23, 26, 27, 29, 31-34]. In this case, the Mre11-Rad50-Nbs1 (MRN) and Rad9-Rad1-Hus1 (9-1-1) complexes are two major DNA damage sensors in the DDR pathway that detect DNA DSBs and single-strand breaks (SSBs), respectively [35-37]. Once rapidly recruited to the sites of DNA lesions following DNA damage, the MRN and 9-1-1 complexes activate the members of the phosphatidylinositol 3-kinase-like protein kinase (PIKK) family, including the ataxia telangiectasia-mutated (ATM), ATM and Rad3 related (ATR), and DNA-dependent protein kinase (DNA-PK), to phosphorylate numerous downstream targets involved in DNA repair and checkpoint pathways [37-44]. Generally, ATM and DNA-PK primarily respond to DNA DSBs, whereas ATR is activated by single-stranded DNA and stalled DNA replication forks [42-44]. One of the critical targets of PIKK phosphorylation is histone H2AX, which is rapidly phosphorylated on serine 139 following DNA damage [45-47]. Phosphorylated

H2AX, termed γ -H2AX, acts as a landing pad for the recruitment of chromatin remodeling complexes and DNA repair factors to the sites of DNA lesions, for subsequent DNA repair through multiple highly conserved signaling pathways [48-53].

In eukaryotic cells, DNA is wrapped within a complex of eight histone molecules, two copies of each of H2A, H2B, H3, and H4, to form nucleosomes [32]. Nucleosomes, together with other proteins, are further assembled into arrays of multiple higher levels of organization to form chromatin [54]. By its very nature, higher order chromatin structure poses a formidable obstacle to the DNA repair machinery gaining access to the DNA lesions, thus limiting the strength of the DDR [29, 55]. Consequently, remodeling of the chromatin landscape is essential and vital for efficient DNA repair [34, 50, 56-59].

Consistent with this notion, it has been well established that chromatin structure is tightly remodeled following the DNA damage through two major mechanisms, ATP-dependent chromatin remodeling and covalent histone posttranslational modifications [18, 34, 48, 59-67]. The ATP-dependent chromatin remodeling complexes have a common ATPase domain, and utilize the energy of ATP hydrolysis to alter chromatin structure, and thus, enhancing the accessibility of the DNA repair proteins to DNA lesion sites [61, 64, 68, 69]. According to the sequence homology of the ATPase subunits, there are four major families of chromatin remodelers in eukaryotes, including SWI/SNF (switching/sucrose nonfermenting), ISWI (imitation switch), Mi-2/NuRD (nucleosome remodeling histone deacetylase), and INO80 (inositol requiring) [69-71]. A growing body of evidence has shown that these chromatin remodeling complexes are directly implicated in DDR in both yeast and mammalian cells [52, 53, 68, 72, 73]. For example, in yeast, the INO80 complex acts a downstream target of the Mec1/Tel1 kinases (ATM/ATR in mammals) to enhance global chromatin mobility [39, 74] and is directly involved in DSB repair through interacting with the DNA damage-induced γ -H2AX [52, 53]. In mammals, the SWI/SNF complex facilitates DNA DSB repair through promoting γ -H2AX induction by directly acting on the chromatin [68], and consequently, inactivation or loss of the subunits of the SWI/SNF complex could result in an enhanced DNA damage sensitivity and apoptosis [68, 75, 76]. It is noteworthy to mention that different chromatin remodeling complexes play distinct roles in repair and checkpoint activation [77, 78].

In addition to chromatin remodeling complexes, reversible histone posttranslational modifications are also involved in DDR [32]. One of the intensively studied histone modifications is histone acetylation, which relaxes chromatin condensation and thus, exposes the damaged DNA that can then be recognized by the DNA repair machinery [59]. Indeed, histone acetyltransferase (HAT) and histone deacetylase (HDAC) complexes have been shown to regulate the repair of DSBs [60, 66]. For instance, the HAT p300-mediated acetylation of histone H3 on lysine 56 [79] creates a favorable chromatin environment for DNA repair [80]. Consequently, defects in the acetylation of lysine 56 in histone H3 could lead to enhanced cellular sensitivity to genotoxic agents [80]. In addition, multiple HDACs, such as class I HDACs (HDAC1-3) and class III HDACs (sirtuins in mammals), are also essential for efficient DNA replication and DNA damage control through diverse mechanisms [25, 81-84]. Taken together, the DDR occurs in the context of chromatin and consequently, the chromatin remodeling and histone-modifying complexes play a central

role in the process. In addition, both complexes might act cooperatively to facilitate DSB repair [34, 85], but the underlying mechanisms remain largely unknown.

3 MTA family proteins in the DDR

The MTA family members MTA1, MTA2, and MTA3 are the major components of the Mi-2/NuRD complex, which is composed of multiple subunits including chromodomain helicase DNA binding protein 3 (CHD3, also known as Mi2- α), CHD4 (also known as Mi2- β), HDAC1, HDAC2, retinoblastoma-binding protein P46 (RBAP46), RBAP48, methyl-CpG binding domain protein 2 (MBD2), and MBD3 [86-89]. In particular, the NuRD complex couples chromatin remodeling with histone deacetylase activities [86-89]. Although the functions of the NuRD complex in gene transcription have been well documented [13, 15], only in recent years the role of the NuRD complex in DDR has begun to emerge [16-18, 21, 22, 90-92] (Fig. 1a).

The initial discovery of the functional role for MTA family proteins in DDR was reported in 1999 [93]. In this study, Schmidt et al. found that multiple subunits of the NuRD complex, including MTA1 and MTA2, were associated with the ATR protein kinase [93], a master regulator of DDR and genomic integrity [42], suggesting that the NuRD complex may be involved in DDR [93].

The first direct evidence for the role of MTA1 in DDR was observed in 2009 [17]. During investigation of the regulatory mechanisms for MTA1 protein stability, we found that MTA1 is a DNA damage responsive protein, which is stabilized and activated in response to ionizing radiation (IR) [17]. Mechanically, the E3 ubiquitin-protein ligase constitutive photomorphogenesis protein 1 (COP1; also known as RFWD2 or RNF200) targets MTA1 for its degradation through an ubiquitin-dependent pathway [17]. However, IR triggers an ATM-dependent auto-degradation of COP1 [94], thus abrogating the ability of COP1 to ubiquitinate and degrade MTA1. Consequently, IR stabilizes and activates MTA1 through an ATM-COP1 pathway. More interestingly, MTA1 can also destabilize COP1 by promoting its auto-ubiquitination [19], thus establishing a double-negative feedback loop between the MTA1 and COP1 for controlling each other's protein stability. Moreover, we found that MTA1-null mouse embryonic fibroblasts were hypersensitive to IR exposure [17]. In support of our findings, a separate study from the Elledge laboratory demonstrated that depletion of MTA1 by small interfering RNAs can indeed render human cancer cells hypersensitive to IR-induced damage [16]. Together, these findings suggest that MTA1 status might be critical for an efficient DSB repair, and it may be involved in IR resistance [16, 17]. Mechanistically, MTA1 interjects into both p53-dependent and -independent DNA repair pathways. In this case, MTA1 regulates p53 stability through inhibiting its ubiquitination by the E3 ubiquitin ligases mouse double minute 2 (MDM2) and COP1, thus activating the p53-dependent transcription program to repair the damaged DNA [95]. In addition, MTA1 also exerts a p53-independent function in the DDR through modulating the p21^{WAF1}-proliferating cell nuclear antigen pathway [21].

In addition to its role in the IR-induced DDR, MTA1 also made inroads into the ultraviolet (UV)-induced DNA damage pathway [16, 20]. In response to UV irradiation, replication

stress triggers the ATR-mediated checkpoint cascade by phosphorylating a number of downstream substrates including checkpoint kinase (Chk1) [96-98]. In addition, Claspin as an adaptor protein is required for the phosphorylation and activation of Chk1 by ATR [99]. In line with previous observation that MTA1 interacts with ATR [93], we demonstrated that UV irradiation stabilizes MTA1 in an ATR-dependent manner and increases MTA1 binding to ATR [20]. Moreover, MTA1 is required for the activation of the ATR-Claspin-Chk1 pathway following UV treatment, thus regulating the ATR-mediated checkpoint signaling [20]. Consequently, depletion of MTA1 results in a defect in the G2-M checkpoint and increases cellular sensitivity to UV-induced DNA damage [20]. Consistent with our findings, a subsequent study further revealed that MTA1 accumulates at the sites of DNA lesions following UV irradiation in a poly ADP-ribose polymerase (PARP)-dependent manner [16].

In addition to MTA1, MTA2 has also been implicated in DDR. An earlier study by van Haaften and coworkers involving a genome-wide RNA interference screening has identified the *erg-1* gene (the *Caenorhabditis elegans* ortholog of mammalian *MTA2*) as one of the candidate genes that protect animal cells against IR [100]. In mammals, MTA2 has been shown to rapidly accumulate at the sites of DNA damage, and to promote DSB repair and G2/M checkpoint activation following DNA damage [22]. Consistently, knockdown of MTA2 leads to an accumulation of spontaneous DNA damage and renders cells sensitive to IR [22]. In addition, MTA2 is also required for DNA replication and promotes maintenance of replication fork integrity via interacting with Tipin, a protein required for systematic progression of S phase of cell cycle. [101] MTA2-Tipin complex directs polymerase alpha toward chromatin which, in-turn, prevents the formation of reversed forks. [101] Because the MTA2-NuRD complex is often associated with heterochromatin maintenance, the MTA2-Tipin complex has been shown to be essential for the replication of centromeric DNA [101]. In contrast, silencing of MTA3 expression by short hairpin RNAs did not alter cellular radiosensitivity [102]. Together, these findings suggest a conserved role for MTA1 and MTA2, but not MTA3 in the DDR signaling.

4 Other subunits of the NuRD complex in the DDR

Several lines of evidence have shown that HDAC1 and HDAC2 are rapidly recruited to the sites of damaged DNA to promote hypoacetylation of lysine 56 in histone H3 and nonhomologous end-joining repair [83]. HDAC1 and HDAC2 are also involved in the maintenance of nascent chromatin structures and regulate the ATM activation and SMARCA5 chromatin-remodeler function in response to the DNA damage [103, 104]. Consistently, HDAC1- and 2-depleted cells are hypersensitive to DNA-damaging agents and show a sustained DNA-damage signaling and increased genomic instability [82, 83, 103]. In addition, the chromatin-remodeling factor CHD4 facilitates both checkpoint signaling and repair events after DNA damage [22, 90, 92, 105-108]. Consequently, knockdown of CHD4 sensitizes cells to DNA damage agents and deregulates cell cycle progression [90, 92]. Interestingly, a recent study using the whole-exome sequencing revealed frequent mutations in CHD4 in the uterine serous carcinoma [109]. Thus, these alterations in the *CHD4* gene might contribute to the development and progression of uterine serous carcinomas by deregulating CHD4-mediated DDR pathway.

5 Conclusions and perspectives

It is becoming increasingly clear that the MTA/NuRD complex, like other chromatin remodeling complexes, plays a conserved role in the DDR pathways, although it appears that MTA family proteins have distinct roles in the process [16,17, 19-22, 102]. As described in Fig. 1b, in response to DNA damage, the MTA family proteins are rapidly recruited to the sites of damaged DNA in a PARP-dependent manner [16]. The MTA family proteins establish a transient repressive chromatin structure to block transcription or activate cell-cycle checkpoint pathway to facilitate DNA repair [16]. In addition, the MTA family proteins associate with the PIKK kinases such as ATR to promote H2AX phosphorylation. Subsequently, phosphorylated H2AX recruits chromatin remodeling complexes and DNA repair proteins to the sites of DNA lesion for an efficient DNA repair. Consequently, the MTA family proteins are required for the repair of the damaged DNA and cell survival following DNA damage. These events in turn, contribute to the development of resistance of cancer cells to DNA damaging radio- and chemotherapies.

Although some advances have been made in our understandings of the emerging role for the MTA family proteins in DDR during the past decade, numerous questions remain to be answered in the near future. For instance, whether and how do MTA proteins cooperate with other subunits within the NuRD complex and other chromatin-modifying factors to induce changes in chromatin close to sites of DNA lesion, and how does this influence DNA repair process? What is the mechanism for PARP-dependent recruitment of the MTA family proteins to the sites of DNA damage, and how do the MTA family proteins make a choice to initiate the transcription program, cell-cycle checkpoint pathway, or DNA repair process? Given that as a part of the NuRD complex, the MTA family proteins interact directly with the histone H3 tail [110], do the MTA family proteins write, read, or erase histone markers during DDR? In addition, it has been shown that the NuRD complex is localized to heterochromatin and involved in heterochromatin maintenance and assembly [108], and that ATM signaling is specifically required for DSB repair within heterochromatin [111]. Thus, does ATM phosphorylate the MTA family proteins to increase the accessibility to heterochromatic DNA breaks? Is there any crosstalk between the MTA family proteins and other heterochromatin-associated proteins such as the heterochromatin protein 1 (HP1) during the DDR? Together, future studies to address these and other molecular detailed events by which the MTA proteins contribute to the DNA damage response are essential.

Finally, the resistance to radiotherapy and chemotherapy is a major problem facing current cancer therapy [112]. Given that the MTA family proteins, especially MTA1, have been shown to be overexpressed in various types of human cancers [2, 14, 112], any aberrant activation of MTA oncogenic pathway might enable cancer cells to survive DNA damage as well as to develop resistance to DNA damaging anticancer treatments [16,17,113]. Therefore, targeting MTA1 would not only suppress tumor progression but also greatly sensitize cancer cells to DNA damage-based radio- and chemotherapies.

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Fig. 1.

Emerging role for the MTA family proteins in the DNA damage response pathway. **a** Timeline of major advances in the roles of MTA family proteins in DDR. **b** Working model summarizing the recent findings related to the role of MTA family proteins in DDR (see the text in details). *DDR* DNA damage response, *MTA* metastasis-associated protein, *PARP* poly ADP-ribose polymerase, *PIKK* phosphoinositide three-kinase-related kinase, *P* phosphorylation