Published in final edited form as:

Cancer Metastasis Rev. 2014 December ; 33(4): 869–877. doi:10.1007/s10555-014-9514-4.

Physiological functions of MTA family of proteins

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Abstract

Although the functional significance of the MTA family of chromatin remodeling proteins in the pathobiology of cancer is fairly well recognized, the physiological role of MTA proteins continues to be an understudied research area and is just beginning to be recognized. Similar to cancer cells, MTA1 also modulates the expression of target genes in normal cells either by acting as a corepressor or coactivator. In addition, physiological functions of MTA proteins are likely to be influenced by its differential expression, subcellular localization and regulation by upstream modulators and extracellular signals. This review summarizes our current understanding of physiological functions of the MTA proteins in model systems. In particular, we highlight recent advances of the role MTA proteins play in the brain, eye, circadian rhythm, mammary gland biology, spermatogenesis, liver, immunomodulation and inflammation, cellular radio-sensitivity, and hematopoiesis and differentiation. Based on the growth of knowledge regarding the exciting new facets of the MTA family of proteins in biology and medicine, we speculate that the next burst of findings in this field may reveal further molecular regulatory insights of non-redundant functions of MTA coregulators in the normal physiology as well as in pathological conditions outside cancer.

Keywords

MTA proteins; Physiological functions; Chromatin remodeling; NuRD complex; Normal cells; Disease models

1 Introduction

The *Mta1* gene, the first discovered member of the MTA family of genes, was identified as a differentially expressed gene in rat mammary gland metastatic and human breast cancer cell lines [1, 2]. Accordingly, our current understanding of the biological functions of the MTA family is predominantly derived from cancer based model systems. However, our understanding of MTAs physiological roles has begins to expand more recently as a number of studies have detected MTA1 expression in most normal tissues and demonstrated that certain tissues express a substantially higher amount of MTA1 [1, 3–5]. To grasp the possible biological roles of MTA1 in mammals, studies involving subcellular expression of MTAs

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Conflict of Interest Statement: The authors declare no any potential conflict of interest.

have been particularly insightful. With regards to expression in organ systems, although MTA1 is expressed in the nervous, endocrine, reproductive, immune, urinary, digestive, and sensory organ systems, its expression is particularly high in certain organs (i.e. murine liver, testes, brain and kidney) [1, 3–5]. This suggests that MTA1 may potentially exhibit tissue specific functions in certain organ systems in mice. Although the functional significance of MTA1 in the pathobiology of cancer is fairly well recognized, the physiological role of MTA1 continues to be an understudied research area and the focus of this review.

The MTA family has been closely associated with the Mi2/NuRD nucleosomal remodeling complexes [6]. The first clue about a previously unknown function of MTA1 in chromatin remodeling came from the experiments performed in Wang's laboratory in 1998 showing the presence of MTA1 in the NuRD complex [7]. This was followed by purification of the NuRD complex by the Reinberg's laboratory, who detected the unexpected presence of MTA2—and not MTA1—in the complex [8]. In general, different MTA family members exist in exclusive NuRD complexes and do not coexist in the same complex [9]. These findings led to the notion that the specialized, non-redundant functions relating to the NuRD complexes that contained distinct MTA family members might be linked to the exclusiveness of the MTA family in a given complex [9–11]. Another recent advance in the field is the structural insights of MTA1 domains to the MTA1-NuRD corepressor complex [12]. In addition to the established corepressor activity of the MTA1-NuRD complex, MTA1 also acts as a coactivator in a NuRD-independent manner, a property that other MTA family members have not been demonstrated to exhibit [6]. Interestingly, the nature of such co-regulatory complexes are influenced by signaling-dependent post-translational modifications on MTA1 protein (Fig. 1A).

Because of the fundamental importance of chromatin remodeling in the regulation of gene expression, any alteration in the physiological levels of MTA family members—due to its gene expression, protein stability or both—is expected to influence the expression of its target genes, and hence, the resulting functions in normal cells, tissues and general physiology. Furthermore, physiological functions of MTA proteins are also likely to be influenced by extracellular signals that might influence subcellular localization. In this context, this review will attempt to summarize our current knowledge and postulate physiological functions of the MTA family with a particular emphasis on MTA1 in various experimental model systems.

2 MTA proteins in the lower vertebrates

Because the Mi2/NuRD complexes are evolutionarily conserved and have housekeeping functions, the existence of MTA homolog across the phylogenetic tree suggests potential significance of MTA homologous genes in invertebrates and the lower vertebrates [10, 11]. Phylogenetic analysis shows that MTA1 like proteins exist throughout the metazoan lineage and are found in highly studied model invertebrate systems—*C. elegans* and *D. melanogaster*. For example, *egl-27* and *egr-1* in *C. elegans* have domain organization similar to MTA1 in mammals [13, 14]. Physiologically, *egl-27* and *egr-1* are involved in embryonic development of *C. elegans*, and its experimental inactivation leads to an abnormal patterning of the embryo [13, 14]. Similarly, the EGL-27 protein complex

modulates the activity of transcription factors with roles in embryonic patterning [15]. Another mechanism through which EGL-27 and EGL-1 proteins block vulval development and participate in embryogenesis is through interaction with NuRD complexes. The EGL-27 interactions enforce repression of vulval target genes in the synMuvA pathway by modifying the local histone deacetylation [16]. The *Egr-1* gene is also closely related to *Drosophila*, chordate and higher vertebrate MTA1.

However, during the course of evolution, MTA proteins diverged into three members (MTA1, MTA2 and MTA3) in vertebrates. MTA1 and MTA3 might have evolved later, from ancestral MTA2, followed by possible gene duplication events [10]. In fact, analysis of Mi-2 complex from lower vertebrates like amphibian *X. laevis*, showed the presence of an MTA-like protein which was later recognized as an ortholog of mammalian MTA2 [10]. Due to its evolutionary conservation in invertebrates, chordates and lower vertebrates, the MTA family might have acquired more complex biological roles in higher vertebrates. We discuss below a few examples of MTAs biological role in distinct cellular processes.

3 MTA proteins in mammals

3.1 MTA1 in brain functions

Although we noticed a relatively high MTA1 expression in the mouse brain [3–5], the potential role of MTA1 in the brain remained unrecognized until the generation of MTA1^{−/−} mice. Our quest in this area was also initially driven by finding that endogenous MTA1 complexes could be effectively pulled down along with DJ1 (or PARK7), a protein related to Parkinson's disease [17]. Because of an established role of DJ1 in controlling the expression of tyrosine hydroxylase (TH) and availability of a MTA1^{−/−} mice, we explored a potential role of MTA1 in the regulation of *TH* expression in the human neuronal cell line and mouse brain. The functional implication of the loss of MTA1 was revealed using the MTA1^{−/−} mice model. Subsequently, these studies led to the observation that MTA1 acts as a coactivator for *TH*-transcription [18]. MTA1 achieves the noted coactivator activity via its direct interaction with DJ1 and the formation of the DJ1-MTA1-RNA polymerase II complex. However, the functionality of the MTA1/DJ1 coactivator complex requires the Pitx3 homeodomain transcription factor to facilitate its recruitment onto the *TH* promoter (Fig. 1B). Consistent with a coactivator function of MTA1 on *TH*, the MTA1^{−/−} mice exhibited a lower *TH* expression and dopamine production in the brain as well as disoriented locomotor skills [18]. These observations shed light on a novel biological role for MTA1 in the brain: supporting the hypothesis of polygenic regulation of a disease-causing gene.

The differential MTA1 expression in the brain of adult mice has also been implicated in aging [19]. Similar to MTA1 interaction with ER-alpha in breast cancer cells, MTA1 interacts with the ER-alpha's transactivation domain in the young adult mouse brain. The authors noticed a progressive loss of such interactions as well as MTA1's expression with age, and suggested that MTA1 may affect the status of ER-alpha signaling in the brain [19]. In another study, MTA1 has been shown to interact with endophilin-3 through SH3 domains of two proteins. Similar to *Mta1*, the levels of *endophilin-3* transcript are higher in the brain and testes. Because endophilin-3 predominantly localizes in the cytoplasm and participates in the process of endocytosis, the noted MTA1-endophilin-3 interaction has been proposed

to influence the process of endocytosis in the brain [20]. In addition to MTA1, both MTA2 and MTA3 may also have some role in the brain. For example, MTA2 interacts with the A +U-rich element-binding factor 1 (AUF1) in developing cortical neurons. Because AUF1 is believed to also regulate transcription in addition to mRNA stability, the AUF1-MTA2/HDAC1 interactions have been proposed to modulate epigenetic signals in the cortex [21]. As opposed to *Mta1* mRNA, the mouse brain is known to express two different transcripts of *Mta3* of approximately 2- and 6.2-kb [22]. Interestingly, MTA3 is a component of a brain-restricted homolog (CHD5) to Mi2 chromatin remodeling complex in rats, which has been implicated in the regulation of neuronal genes with a possible role in aging and Alzheimer's disease [23].

3.2 MTA1 in eye functions

During an investigation involving MTA1 regulation of a homeobox containing DNA-binding factor *Six3*—a transcription factor known for eye and retinal development [24]—we noticed that MTA1 acts as a corepressor of *Six3*-transcription and that genetic depletion of *Mta1* leads to increased *Six3* expression in the eyes from MTA1^{−/−} mice [25]. While assaying the status of cell specific markers, we also noticed an increased rhodopsin staining in the retina from MTA1^{−/−} mice as compared to the levels in wild-type mice [25]. Rhodopsin is an important component of the phototransduction pathway and is crucial for vision under low light conditions. Because the levels of both *Six3* and rhodopsin were increased in the retina from MTA1^{−/−} mice, these observations raised an interesting possibility that *Six3* might be a coactivator of *rhodopsin*-transcription. Results from mechanistic studies suggested that MTA1 modulates the expression of rhodopsin by acting as a repressor of *Six3* and that *Six3* binds to *rhodopsin*-promoter to stimulate its transcription (Fig. 1C). Interestingly, *Six3* also cooperates with previously known coactivators NRL and CRX1 to stimulate rhodopsin transcription [26, 27]. The MTA1^{−/−} mice exhibited an increased *Six3* expression with rhodopsin expression and associates with a healthy retina. These findings suggested a potential role of chromatin remodeling activity of MTA1 in the eye via regulating the *Six3*-rhodopsin pathway. Because mutations in *Six3* gene has been linked with non-syndromic holoprosencephaly, an abnormality in brain formation in humans [28], the revelation of the *Six3*-rhodopsin pathway raises an interesting speculation of a potentially defective rhodopsin pathway in holoprosencephaly patients with *Six3* mutations.

3.3 MTA1- a new component of biologic clock

While searching for clues about physiological regulators of MTA1, we noticed the presence of an evolutionarily conserved canonical E-box motif (CACGTG) in the mouse *Mta1*-promoter. Because genes with E-box were likely to represent clock-controlled genes, we explored the hypothesis that MTA1 may be a component of the circadian clock. Evidences from MTA1^{−/−} mice provided support for a role of MTA1 in circadian rhythm [29]. Genetic depletion of MTA1 in mice disturbs circadian rhythms under constant light and normal entrainment behavior, as evaluated in free running exercises. MTA1 regulates circadian circuits by interacting and recruiting CLOCK-BMAL1 to its own promoter for active transcription. In fact, MTA1 interacts with the CLOCK-BMAL1 complex to either self-regulate its own transcription or stimulate *Cry*-transcription (Fig. 1D). Once MTA1 level is

induced, it impairs the CRY1 mediated negative feedback loop. This study unfolds a novel role of MTA1 in modulating the biological clock through a positive feedback over the circadian machinery.

3.4 Role in heart development

The development of embryonic heart is mediated by a number of transcriptional factors, including FOG2. FOG2 acts by repressing GATA4 transcription factor-dependent expression of target genes. FOG2 achieve this function by interacting with the zinc-finger domain of the MTA1 protein and recruit the MTA1-NuRD corepressor complex to the GATA4 target genes [30]. MTA1 silencing impairs FOG2-dependent repression of GATA4 target genes. In brief, MTA1 controls FOG2-dependent GATA4 activity through the NuRD repressor complex, and thus, contribute to embryonic heart development in a mouse model [30].

3.5 MTA proteins in mammary gland biology

Among the MTA family members, MTA1 and MTA3 have been shown to display opposite expression during the development of mammary gland tumors, starting with distinct sub-cellular localization in normal mammary ducts. For example, the expression of MTA1 and MTA3 is progressively increased and reduced, respectively, during tumor progression in a mouse model system [31]. Likewise, MTA1 was primarily localized in the nucleus of a small percentage of epithelial cells while MTA3 expression was detected in the cytoplasm and nuclear compartment of more epithelial cells [31].

Both normal development as well as oncogenesis of the mammary gland is profoundly influenced affected by the Wingless 1 (Wnt1) and its target genes. Because Wnt1 expression is known to be directly repressed by Six3 DNA-binding protein in the retinal and neuronal cells [32], and because MTA1 represses *Six3*-transcription in the retinal cells [25], we explored the hypothesis of MTA1 regulation of Wnt1 in the mammary epithelial cells and breast cancer cells. We found that MTA1 stimulates the expression of Wingless 1 (Wnt1) via repressing the transcription of its endogenous inhibitor Six3 [33]. We also demonstrated that depletion of the endogenous MTA1 in breast cancer cells upregulates the expression of Six3 while depletion of Six3 in mammary epithelial cells stimulates Wnt1 expression [33]. To deduce the significance of these findings in physiological relevant models, we next examined the status of MTA1-Six3-Wnt1 pathway in mammary glands from MTA1^{-/-} mice. To our surprise, we observed that the depletion of MTA1 in mammary gland was accompanied by upregulation of Six3 expression, downregulation of β -catenin (a Wnt1 signaling target) as well as hypobranched of mammary glands from MTA1^{-/-} mice as compared to mammary glands from wild-type mice [33]. Collectively, these results revealed a physiologic role of MTA1 as a novel upstream regulator of the Wnt1 pathway.

In addition to MTA1, MTA3 has been also shown to participate in mammary gland development as MTA3 overexpression in mouse mammary gland leads to defective side branching in virgin as well as in early pregnant female mice [34]. The mature mammary glands in MTA3 transgenic mice lack secondary and tertiary ductal branching and correlated with repressed Wnt4 expression in MTA3 transgenic mice as well as inhibition of β -catenin

and Wnt-responsive genes in experimental systems [34]. In brief, MTA3-NuRD complex inhibits mammary gland development by suppressing Wnt4 signaling in a HDAC dependent manner.

3.6 MTA proteins in spermatogenesis

Because the testes are one of few organs that have very high levels of MTA1 and the male germ cells express abundant MTA1 [35–37], MTA1 is believed to have a potential regulatory role in spermatogenesis. In humans, MTA1 is largely dense around the nucleus of round spermatids and primary spermatocytes. Interphasic mouse spermatocytes undergoing leptotene, zygotene and pachytene stages exhibit an intense nuclear staining. The stage-specific differential expression of MTA1 during testes development is suggestive of its potential significance during spermatogenesis. MTA1 has also been shown to protect spermatogenic tumor cells against hyperthermia-induced apoptosis through its interaction with p53 during gametogenesis [35–37]. Further, MTA1-depletion in spermatogenic tumor cells increases p53-acetylation [37], suggesting that MTA1 may be a negative regulator of p53 activity due to MTA1-NuRD associated HDAC activity to influence apoptosis threshold after hyperthermia. Another member of the MTA family, MTA2, is induced by testosterone as well as by follicle-stimulating hormone (FSH) in Sertoli cells. Once induced, MTA2 also represses the transcription of the FSH receptor in FSH stimulated cells as a part of a negative feedback regulatory loop [38]. Consistent with this pathway, experimental downregulation of MTA2 impairs the FSH-mediated downregulation of the FSH receptor [38].

More recently, the expression of MTA1 and MTA1s has been shown to increase with gestation in rat placentas and MTA1's colocalization with estrogen receptor [39]. This raises the possibility that MTA1 may potentially regulate chromatin remodeling of its target genes in placenta and placental functions. Further, based on the lessons of corepression of ER by MTA1 in breast cancer, it will be important to determine the influence of MTA1 and MTA1s in genomic and non-genomic effects of estrogen during pregnancy. These observations highlight the potential significance of MTA1 and MTA2 in reproductive biology.

3.7 Role in cell cycle in ovary

The MTA3 is highly expressed in the nucleus of granulosa cells within ovarian follicles and corpus luteum in female mice. MTA3 promotes cell proliferation in ovaries by interacting and subsequently recruiting the NuRD components such as CHD4 and HDAC1 to regulate gene transcription [40]. Additionally, MTA3 also interacts with the core cohesion complex protein RAD21 to facilitate cell division in ovaries. MTA3 depletion in mouse primary granulosa cells resulted in decreased proliferation which could be effectively rescued by MTA3 overexpression. Interestingly, MTA3-deficient granulosa cells show a significant accumulation of cells in the G2-M phase, revealing that MTA3 is essential for the progression of cells through the cell cycle [40].

3.8 MTA proteins in immunomodulatory responses

Interestingly, MTA1 has been shown to modulate inflammatory responses and acts both as a target of NF- κ B signaling as well as a component of NF- κ B signaling. For example, stimulation of macrophages with *Escherichia coli* lipopolysaccharide (LPS) leads to transcriptional activation of MTA1 via the NF- κ B pathway. The relevance of MTA1 in inflammatory signaling was made evident by studies showing that MTA1 depletion inhibits the ability of LPS to induce NF- κ B signaling and cytokines in macrophages [41]. Unexpectedly, MTA1 manifests its dual coregulatory activity in the inflammatory response: under basal condition, MTA1 represses the expression of target cytokine genes while acting as an coactivator of cytokines in LPS-stimulated macrophages [41]. Additionally, LPS stimulation of macrophage is accompanied by increased expression of cytokines [42]; MTA1 also stimulates the expression of transglutaminase 2 - a crosslinking enzyme involved in immediate defense during injury or infection in LPS-stimulated cells [43]. These observations raise an interesting possibility that MTA1 expression is likely to be induced by extracellular signals which themselves induce NF- κ B signaling pathway. Further, because NF- κ B signaling plays an inherent role in the expression of pro- and anti-inflammatory cytokines, MTA1 is postulated to be an upstream modulator of inflammation and immunologic responses.

MTA2 has been implicated as a critical player in T cell mediated immunity. Results from the surviving MTA2^{-/-} mice develop autoimmune traits and elevated circulating autoantibodies. Upon stimulation, T lymphocytes from MTA2^{-/-} mice elicit increased expression of IL-2, IL-4 and IFN- γ [44], possibly due to the loss of corepressive activity of the GATA3-MTA2 complex [44, 45]. In this model, MTA2 acts against GATA3 for cytokine promoters resulting in elevated Th2 cytokine. These findings elucidate that MTA2 may be involved in rewiring cytokine signaling along the Th2 axis for T helper cell differentiation.

3.9 MTA1 in cellular radio-sensitivity

While searching for possible clues about the stability of the MTA1 protein, it was noted that the endogenous levels of MTA1 are rapidly elevated in mouse fibroblasts and cancer cells as well as in mice (i.e., mammary gland, the skin and thymus gland) upon exposure to ionizing radiation [46]. Because there was no change in the levels of MTA1 mRNA, a large body of experimental studies suggested that MTA1 is a DNA-damage responsive protein and its stability is regulated by COP1 E3-ligase in a manner dependent on the ATM kinase [46]. These early findings open up the possibility of MTA1 undisclosed role in DNA-damage response as a cascade of DNA repair pathways. In fact, genetic [46] and experimental depletion of MTA1 [47] have been shown to promote the sensitivity of target cells to a better survival upon DNA-damage stress. Additional mechanistic studies suggested that MTA1 participates in both p53-dependent and p-53-independent mechanisms of DNA repair [48, 49]. Surprisingly, MTA1 represses the expression of the *p21WAF1*—one of the most characterized p53-target genes—in a p53-independent manner, as the levels of p21WAF1 are induced in MTA1^{-/-} fibroblasts despite the marginal increase in the levels of p53 by ionizing radiation [50].

A large number of genes belonging to multiple cellular functions are influenced by MTA1 in both p53-dependent and p53-independent manners. For example, the two most affected canonical pathways of the *Mta1*-regulated but p53-independent genes belong to inflammation and cancer signaling [50]. In addition to ionizing radiation, MTA1 also participates in ultraviolet (UV) triggered DNA-damage response. Exposure of cells to UV also stabilizes the MTA1 protein through functional interactions of ATR (ataxia telangiectasia- and Rad3-related) kinase and Chk1 (checkpoint kinase 1) [51]. Based on these results, it is postulated that endogenous levels of MTA1 level may act as a determinant of radio-sensitivity of cells and provide a possible protective role against spontaneous DNA-damage and stress signals. Therefore, a future targeting of MTA1 itself or a specific inspection of MTA1's biochemical roles will not only shed light of MTAs participation in cancer pathways, but could also be exploited to modify the radio-sensitivity of target cells.

3.10 MTA1 in liver functions

Because the expression of MTA1 is particularly high in rapidly regenerative liver [52], the MTA1 pathway also participates in hepatic regeneration following liver injury. Li *et al* have shown that following a partial hepatectomy in mice, the level of MTA1 elevates in the cytoplasm of liver cells and correlates well with proliferative activity [52]. Moreover, exogenous expression of MTA1 in mice liver leads to a marked expression of cellular indicators of proliferation such as Cyclin-dependent Kinase-1 (CDK1) and Cyclin D [52]. These studies suggest an unappreciated role of MTA1 in hepatic proliferation and differentiation during pathological liver injury. In addition, MTA1 could also influence liver function—both under basal or triggered responses—by regulating the expression of immuno-modulatory cytokines. This is exemplified by observations showing an influence of MTA1 status on inflammatory response against pathogens as genetic deletion of *Mta1* in mice modulates the levels of multiple cytokines belonging to Th1 and Th2 responses [53].

3.11 MTA proteins in hematopoiesis and differentiation

In another exciting lead regarding the physiological functions of MTAs comes from the role of MTA2 in erythropoiesis and red blood cell membrane (RBC) integrity. Data from chromatin-based analyses using erythroid and non-erythroid cells suggest an enrichment and co-occupancy of MTA2 along with transcriptional regulators like GATA1 and FOG1 onto the promoters of most RBC membrane proteins in erythroid cell types [54]. Furthermore, MTA2 binding to the GATA1 consensus sequences in promoters of membrane protein genes associated with RBC morphology further link MTA2 to RBC biology [55]. Because some of the RBC membrane proteins could regulate chromatin remodeling, and the dysregulation of RBC membrane proteins are known to be associated with pathologic conditions such as hemolytic anemia, one cannot rule out a role of MTA2 (and perhaps other MTA family members) in blood homeostasis. In this context, another family member, MTA3, has also been shown to modulate hematopoiesis in a model system: MTA3 silencing in Zebra fish embryos blocks hematopoietic cell differentiation and leads to abnormal angiogenesis, a situation which could be somewhat mimicked by the use of HDAC inhibitors [56]. As MTA3 functions as a part of the NuRD complex, the MTA3-NuRD-HDAC1 complex has been shown to modulate the expression of genes responsible for primitive hematopoiesis such as *scl* and *lmo2*. In conclusion, the MTA3-NuRD complex may be indispensable for

commencing hematopoiesis and provides a connecting link for primitive hematopoiesis pathway and blood homeostasis in higher vertebrates [56]. However, more research is needed to follow these early observations.

The MTA1 has been also shown to modulate the differentiation of human mesenchymal stem cells along the osteogenic lineage as this process is profoundly affected by knocking down endogenous MTA1. Experimental depletion of MTA1 in human mesenchymal stem cells leads to increased calcium deposition as well as expression of osteogenic markers, including bone sialoprotein, osteocalcin and collagen type I etc [57]. This study points to a potentially, yet-to-be discovered function of MTA1 in bone remodeling and differentiation that uses more complex model cellular models and whole animal models.

4 Conclusions and perspectives

Owing to an inherent importance of MTA-chromatin remodeling complexes in gene transcription and differential expression of MTA proteins in certain organ systems, the MTA family of proteins is believed to exert physiological functions via modulating the levels of their target gene products and their associated functions. In addition, the levels of *Mta* transcripts and stability of MTA1 are changed by extracellular signals either directly or indirectly through modifying enzymes, epigenetic components and DNA-binding factors. Therefore, any natural or signal-dependent perturbations in such molecules could potentially impact the steady states of the MTA family of proteins and, hence, the resulting physiological functions. Many of the biological functions of regulatory proteins such as the MTA family are likely to be further governed by their subcellular localizations and dynamic change in response to extracellular signals. Because the levels of MTA1 are not only high in rapidly-regenerating tissues such as liver and testes, but are also in tissues with low or no proliferative potential such as brain and kidney, it is obvious that MTA1 physiological functions are not necessarily intimately connected with the proliferative potential of the cell-types in question. We have attempted to illustrate this unique property of MTA1 by a few examples of physiological functions in experimental model systems (Fig. 2) in the preceding paragraphs in this review. The current data also imply that the nature of upstream signals and/or determinants of expression of the MTA family of proteins is expected to be different in the target organ systems.

Based on the growth of exciting new facets of the MTA family of proteins in biology and medicine since the first MTA1 publication in 1994, it is tempting to speculate that the next burst of findings in this area may reveal the significance of the MTA family of regulatory proteins in both normal physiological functions as well as pathological conditions outside cancer. One of the major challenges for this goal is to take findings from experimental model systems to large vertebrates and humans. It is our hope that the MTA field will continue to generate ever greater interest in academic and therapeutic-based laboratories scientists.

Acknowledgments

We apologize for not citing many other deserving studies from our colleagues due to space limitations. We thank fellows, research staff and colleagues in the Kumar laboratory for their contribution to the biology of MTA1 in human cancer. The MTA1 project in Kumar's lab is supported by NIH grant CA098823.

References

1. Toh Y, Pencil SD, Nicolson GL. A novel candidate metastasis-associated gene, mta1, differentially expressed in highly metastatic mammary adenocarcinoma cell lines. cDNA cloning, expression, and protein analyses. *J Biological Chemistry*. 1994; 269(37):22958–22963.
2. Toh Y, Pencil SD, Nicolson GL. Analysis of the complete sequence of the novel metastasis-associated candidate gene, mta1, differentially expressed in mammary adenocarcinoma and breast cancer cell lines. *Gene*. 1995; 159(1):97–104. [PubMed: 7607577]
3. Mazumdar A, Wang RA, Mishra SK, Adam L, Bagheri-Yarmand R, Mandal M, et al. Transcriptional repression of oestrogen receptor by metastasis-associated protein 1 corepressor. *Nature Cell Biology*. 2001; 3(1):30–37.
4. Li W, Ma L, Zhao J, Liu X, Li Z, Zhang Y. Expression profile of MTA1 in adult mouse tissues. *Tissue Cell*. 2009; 41(6):390–399. [PubMed: 19524276]
5. Liu J, Xu D, Wang H, Zhang Y, Chang Y, Zhang J, et al. The subcellular distribution and function of MTA1 in cancer differentiation. *Oncotarget*. 2014; 5(13):5153–5164. [PubMed: 24970816]
6. Li DQ, Pakala SB, Nair SS, Eswaran J, Kumar R. Metastasis-associated protein 1/nucleosome remodeling and histone deacetylase complex in cancer. *Cancer Research*. 72(2):387–394. [PubMed: 22253283]
7. Xue Y, Wong J, Moreno GT, Young MK, Cote J, Wang W. NURD, a novel complex with both ATP-dependent chromatin-remodeling and histone deacetylase activities. *Molecular Cell*. 1998; 2(6):851–861. [PubMed: 9885572]
8. Zhang Y, Ng HH, Erdjument-Bromage H, Tempst P, Bird A, Reinberg D. Analysis of the NuRD subunits reveals a histone deacetylase core complex and a connection with DNA methylation. *Genes & Development*. 1999; 13(15):1924–1935. [PubMed: 10444591]
9. Yao YL, Yang WM. The metastasis-associated proteins 1 and 2 form distinct protein complexes with histone deacetylase activity. *Journal Biological Chemistry*. 2003; 278(43):42560–42568.
10. Bowen NJ, Fujita N, Kajita M, Wade PA. Mi-2/NuRD: multiple complexes for many purposes. *Biochim Biophys Acta*. 2004; 1677(1–3):52–57. [PubMed: 15020045]
11. Denslow SA, Wade PA. The human Mi-2/NuRD complex and gene regulation. *Oncogene*. 2007; 26(37):5433–5438. [PubMed: 17694084]
12. Millard CJ, Watson PJ, Celardo I, Gordiyenko Y, Cowley SM, Robinson CV, et al. Class I HDACs share a common mechanism of regulation by inositol phosphates. *Molecular Cell*. 2013; 51(1):57–67. [PubMed: 23791785]
13. Herman MA, Ch'ng Q, Hettenbach SM, Ratliff TM, Kenyon C, Herman RK. EGL-27 is similar to a metastasis-associated factor and controls cell polarity and cell migration in *C. elegans*. *Development*. 1999; 126(5):1055–1064. [PubMed: 9927605]
14. Zimmerman SM, Kim SK. The GATA transcription factor/MTA-1 homolog egr-1 promotes longevity and stress resistance in *Caenorhabditis elegans*. *Aging Cell*. 2014; 13(2):329–339. [PubMed: 24304470]
15. von Zelewsky T, Palladino F, Brunschwig K, Tobler H, Hajnal A, Muller F. The *C. elegans* Mi-2 chromatin-remodelling proteins function in vulval cell fate determination. *Development*. 2000; 127(24):5277–5284. [PubMed: 11076750]
16. Chen Z, Han M. Role of *C. elegans* lin-40 MTA in vulval fate specification and morphogenesis. *Development*. 2001; 128(23):4911–4921. [PubMed: 11731470]
17. Bonifati V, Rizzu P, van Baren MJ, Schaap O, Breedveld GJ, Krieger E, et al. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science*. 2003; 299(5604):256–259. [PubMed: 12446870]

18. Reddy SD, Rayala SK, Ohshiro K, Pakala SB, Kobori N, Dash P, et al. Multiple coregulatory control of tyrosine hydroxylase gene transcription. *Proc Natl Acad Sci U S A*. 108(10):4200–4205. [PubMed: 21368136]
19. Thakur MK, Ghosh S. Interaction of estrogen receptor alpha transactivation domain with MTA1 decreases in old mouse brain. *J Molecular Neurosciences*. 2009; 37(3):269–273.
20. Aramaki Y, Ogawa K, Toh Y, Ito T, Akimitsu N, Hamamoto H, et al. Direct interaction between metastasis-associated protein 1 and endophilin 3. *FEBS Lett*. 2005; 579(17):3731–3736. [PubMed: 15978591]
21. Lee C, Gyorgy A, Maric D, Sadri N, Schneider RJ, Barker JL, et al. Members of the NuRD chromatin remodeling complex interact with AUF1 in developing cortical neurons. *Cereb Cortex*. 2008; 18(12):2909–2919. [PubMed: 18413351]
22. Simpson A, Uitto J, Rodeck U, Mahoney MG. Differential expression and subcellular distribution of the mouse metastasis-associated proteins Mta1 and Mta3. *Gene*. 2001; 273(1):29–39. [PubMed: 11483358]
23. Potts RC, Zhang P, Wurster AL, Precht P, Mughal MR, Wood WH 3rd, et al. CHD5, a brain-specific paralog of Mi2 chromatin remodeling enzymes, regulates expression of neuronal genes. *PLoS One*. 6(9):e24515. [PubMed: 21931736]
24. Del Bene F, Tessmar-Raible K, Wittbrodt J. Direct interaction of geminin and Six3 in eye development. *Nature*. 2004; 427(6976):745–749. [PubMed: 14973488]
25. Manavathi B, Peng S, Rayala SK, Talukder AH, Wang MH, Wang RA, et al. Repression of Six3 by a corepressor regulates rhodopsin expression. *Proc Natl Acad Sci U S A*. 2007; 104(32):13128–13133. [PubMed: 17666527]
26. Mitton KP, Swain PK, Chen S, Xu S, Zack DJ, Swaroop A. The leucine zipper of NRL interacts with the CRX homeodomain. A possible mechanism of transcriptional synergy in rhodopsin regulation. *J Biological Chemistry*. 2000; 275(38):29794–29799.
27. Qtaishat NM, Wiggert B, Pepperberg DR. Interphotoreceptor retinoidbinding protein (IRBP) promotes the release of all-trans retinol from the isolated retina following rhodopsin bleaching illumination. *Experimental Eye Research*. 2005; 81(4):455–463. [PubMed: 15935345]
28. Wallis DE, Roessler E, Hehr U, Nanni L, Wiltshire T, Richieri-Costa A, et al. Mutations in the homeodomain of the human *SLX3* gene cause holoprosencephaly. *Nature Genetics*. 1999; 22(2):196–198. [PubMed: 10369266]
29. Li DQ, Pakala SB, Reddy SD, Peng S, Balasenthil S, Deng CX, et al. Metastasis-associated protein 1 is an integral component of the circadian molecular machinery. *Nature Communication*. 2013; 4:2545.
30. Zhou B, Ma Q, Kong SW, Hu Y, Campbell PH, McGowan FX, Ackerman KG, Wu B, Zhou B, Tevosian SG, Pu WT, et al. Fog2 is critical for cardiac function and maintenance of coronary vasculature in the adult mouse heart. *J Clinical Investigation*. 2009; 119(6):1462–1476.
31. Zhang H, Stephens LC, Kumar R. Metastasis tumor antigen family proteins during breast cancer progression and metastasis in a reliable mouse model for human breast cancer. *Clinical Cancer Research*. 2006; 12(5):1479–1486. [PubMed: 16533771]
32. Lagutin OV, Zhu CC, Kobayashi D, Topczewski J, Shimamura K, Puelles L, et al. Six3 repression of Wnt signaling in the anterior neuroectoderm is essential for vertebrate forebrain development. *Genes & Development*. 2003; 17(3):368–379. [PubMed: 12569128]
33. Kumar R, Balasenthil S, Manavathi B, Rayala SK, Pakala SB. Metastasis-associated protein 1 and its short form variant stimulates Wnt1 transcription through promoting its derepression from Six3 corepressor. *Cancer Research*. 70(16):6649–6658. [PubMed: 20682799]
34. Zhang H, Singh RR, Talukder AH, Kumar R. Metastatic tumor antigen 3 is a direct corepressor of the Wnt4 pathway. *Genes & Development*. 2006; 20(21):2943–2948. [PubMed: 17050676]
35. Li W, Zhang J, Liu X, Xu R, Zhang Y. Correlation of appearance of metastasis-associated protein1 (Mta1) with spermatogenesis in developing mouse testis. *Cell Tissue Research*. 2007; 329(2):351–362. [PubMed: 17401724]
36. Li W, Liu XP, Xu RJ, Zhang YQ. Immunolocalization assessment of metastasis-associated protein 1 in human and mouse mature testes and its association with spermatogenesis. *Asian J Andrology*. 2007; 9(3):345–352.

37. Li W, Wu ZQ, Zhao J, Guo SJ, Li Z, Feng X, et al. Transient protection from heatstress induced apoptotic stimulation by metastasis-associated protein 1 in pachytene spermatocytes. *PLoS One*. 6(10):e26013. [PubMed: 22022494]
38. Zhang S, Li W, Zhu C, Wang X, Li Z, Zhang J, et al. Sertoli cell-specific expression of metastasis-associated protein 2 (MTA2) is required for transcriptional regulation of the follicle-stimulating hormone receptor (FSHR) gene during spermatogenesis. *J Biological Chemistry*. 287(48):40471–40483.
39. Al-Bader MD, Kilarkaje N, El-Farra A, Al-Abdallah AA. Expression and Subcellular Localization of Metastasis-Associated Protein 1, Its Short Form, and Estrogen Receptors in Rat Placenta. *Reproductive Sciences*.
40. Kwintkiewicz J, Padilla-Banks E, Jefferson WN, Jacobs IM, Wade PA, Williams CJ. Metastasis-associated protein 3 (MTA3) regulates G2/M progression in proliferating mouse granulosa cells. *Biology of Reproduction*. 2012; 86(3):1–8. [PubMed: 22075476]
41. Pakala SB, Bui-Nguyen TM, Reddy SD, Li DQ, Peng S, Rayala SK, et al. Regulation of NF-kappaB circuitry by a component of the nucleosome remodeling and deacetylase complex controls inflammatory response homeostasis. *J Biological Chemistry*. 285(31):23590–23597.
42. Pakala SB, Reddy SD, Bui-Nguyen TM, Rangparia SS, Bommana A, Kumar R. MTA1 coregulator regulates LPS response via MyD88-dependent signaling. *J Biological Chemistry*. 285(43):32787–32792.
43. Ghanta KS, Pakala SB, Reddy SD, Li DQ, Nair SS, Kumar R. MTA1 coregulation of transglutaminase 2 expression and function during inflammatory response. *J Biological Chemistry*. 286(9):7132–7138.
44. Lu X, Kovalev GI, Chang H, Kallin E, Knudsen G, Xia L, et al. Inactivation of NuRD component Mta2 causes abnormal T cell activation and lupus-like autoimmune disease in mice. *J Biological Chemistry*. 2008; 283(20):13825–13833.
45. Hosokawa H, Tanaka T, Suzuki Y, Iwamura C, Ohkubo S, Endoh K, et al. Functionally distinct Gata3/Chd4 complexes coordinately establish T helper 2 (Th2) cell identity. *Proc Natl Acad Sci U S A*. 110(12):4691–4696. [PubMed: 23471993]
46. Li DQ, Ohshiro K, Reddy SD, Pakala SB, Lee MH, Zhang Y, et al. E3 ubiquitin ligase COP1 regulates the stability and functions of MTA1. *Proc Natl Acad Sci U S A*. 2009; 106(41):17493–17498. [PubMed: 19805145]
47. Chou DM, Adamson B, Dephoure NE, Tan X, Nottke AC, Hurov KE, 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(43):18475–18480. [PubMed: 20937877]
48. Li DQ, Divijendra Natha Reddy S, Pakala SB, Wu X, Zhang Y, Rayala SK, et al. MTA1 coregulator regulates p53 stability and function. *J Biological Chemistry*. 2009; 284(50):34545–34552.
49. Li DQ, Pakala SB, Reddy SD, Ohshiro K, Peng SH, Lian Y, et al. Revelation of p53-independent function of MTA1 in DNA damage response via modulation of the p21 WAF1-proliferating cell nuclear antigen pathway. *J Biological Chemistry*. 285(13):10044–10052.
50. Ghanta KS, Li DQ, Eswaran J, Kumar R. Gene profiling of MTA1 identifies novel gene targets and functions. *PLoS One*. 6(2):e17135. [PubMed: 21364872]
51. Li DQ, Ohshiro K, Khan MN, Kumar R. Requirement of MTA1 in ATR-mediated DNA damage checkpoint function. *J Biological Chemistry*. 285(26):19802–19812.
52. Li W, Zhu H, Bao W, Fu H, Li Z, Liu X, et al. Involvement of metastasis tumor antigen 1 in hepatic regeneration and proliferation. *Cell Physiological Biochemistry*. 2008; 22(1–4):315–326.
53. Nair SS, Bommana A, Pakala SB, Ohshiro K, Lyon AJ, Suttiprapa S, et al. Inflammatory response to liver fluke *Opisthorchis viverrini* in mice depends on host master coregulator MTA1, a marker for parasite-induced cholangiocarcinoma in humans. *Hepatology*. 54(4):1388–1397. [PubMed: 21725997]
54. Steiner LA, Maksimova Y, Schulz V, Wong C, Raha D, Mahajan MC, et al. Chromatin architecture and transcription factor binding regulate expression of erythrocyte membrane protein genes. *Molecular Cellular Biology*. 2009; 29(20):5399–5412. [PubMed: 19687298]

55. Rodriguez P, Bonte E, Krijgsveld J, Kolodziej KE, Guyot B, Heck AJ, et al. GATA-1 forms distinct activating and repressive complexes in erythroid cells. *EMBO J.* 2005; 24(13):2354–2366. [PubMed: 15920471]
56. Li X, Jia S, Wang S, Wang Y, Meng A. Mta3-NuRD complex is a master regulator for initiation of primitive hematopoiesis in vertebrate embryos. *Blood.* 2009; 114(27):5464–5472. [PubMed: 19864643]
57. Kumar A, Salimath BP, Schieker M, Stark GB, Finkenzeller G. Inhibition of metastasis-associated gene 1 expression affects proliferation and osteogenic differentiation of immortalized human mesenchymal stem cells. *Cell Proliferation.* 44(2):128–138. [PubMed: 21401754]

Figure 1. MTA1 coregulator regulates gene expression

A. Dual coregulatory activity of MTA1 regulates diverse cellular pathways. **B.** MTA1 acts as a coactivator of the *tyrosine hydroxylase* (TH) transcription via interacting with DJ1, Pitx3, Pol II and chromatin remodeling proteins. **C.** MTA1-NuRD complex represses *Six3*-transcription which in-turn, modulates *Rhodopsin* expression. **D.** *Mta1* is a target of the Clock/Bmal1 complex and MTA1 acts as a coactivator of its own transcription as well as of *Cry1*-promoter.

Figure 2. Emerging examples of physiological functions of MTA proteins through multiple gene and protein targets in model systems