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Post-transcriptional regulation of MTA family by microRNAs in the context of cancer

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Abstract

MicroRNAs (miRNAs) are a class of 20–24 nt small non-coding RNAs that regulate a wide range of biological processes through changing the stability and translation of their target mRNA genes. Shortly after their identification, many miRNA genes have been found dysregulated in a variety of human cancers, indicating a pathological function of this gene class in mediating cancer progression. Over the past decade, accumulated literature has shown that miRNAs participate in numerous cancer-relevant processes including cell proliferation, apoptosis, differentiation, metabolism and importantly, metastasis, which accounts for the mortality of approximately 90% of cancer patients. Several recent publications have linked miRNAs with metastasis-associated protein (MTA) family members. Given the fact that the MTA family members are widely overexpressed in human cancers and their nature of serving as both corepressor and coactivator in gene regulation, it is intriguing to study whether certain miRNAs regulate cancer progression through modulating the expression of MTA family members. In this review, we will focus on recent advances in understanding the regulatory relationship between certain miRNAs and MTA family members.

Keywords

MicroRNAs; Metastasis-associated proteins (MTAs); Cancer progression

1 miRNAs and cancer

With the development of next-generation sequencing techniques, a previously unrecognized world of non-coding RNA molecules have been recently discovered [1]. MiRNAs, the best-characterized non-coding RNA family with about 1400 members in the human genome, have been shown to involve in almost all the biological processes that have ever been studied [2]. In addition to their important roles in development and maintaining physiological tissue homeostasis [3], dysregulation of miRNAs have been implicated in multiple pathological processes including cancer [4–6]. Decided by the specific cellular

context, miRNAs can either function as oncogenes that overexpressed in tumors to facilitate tumorigenesis or as tumor suppressors that down-regulated in tumors [7–9]. Importantly, many miRNAs have been shown to regulate the metastatic process, which accounts for the mortality of approximately 90% of cancer patients [10,11].

Although there are still debates on certain aspects of miRNA biogenesis and their functional mechanisms, the key processes have been clearly characterized [12]. Majority of miRNAs genes are transcribed by RNA polymerase II, either as an individual transcriptional unit or embedded within the introns of protein-coding genes. These transcriptional products, named as pri-miRNAs, are trimmed inside the nucleus by the microprocessor complex containing RNase III enzyme Drosha, yielding an approximately 70 nt-long precursor (pre-miRNA) with a hairpin structure. Pre-miRNAs are subsequently exported to the cytoplasm by exportin 5 (XPO5), where they are further processed into 19 – 25nt miRNA duplexes by a protein complex containing RNase III protein Dicer. In most cases, the less stable strand in the miRNA duplex is incorporated into the RNA-induced silencing complex (RISC), which contains several key proteins such as Argonaute (Ago) and GW182. The mature miRNA then guides the miRNA-RISC complex to its target mRNA through sequence recognition and induces post-transcriptional gene silencing by tethering RISC to these target mRNAs [13–15].

After human miRNAs were discovered, it was soon noticed that many miRNA genes were located at fragile sites in the genomic region that frequently amplified or deleted in human cancers [16]. In addition, expression analysis using genome-wide microarray and sequencing techniques in a wide spectrum of cancer types have evidenced that aberrant miRNA expression is commonly found in these diseases [5,17]. To answer the question whether the change of miRNA expression is a cause or consequence of cancer progression, multiple groups have provided mechanistic explanations that many miRNAs function as causal genes in cancer development. For example, the miR-17-92 cluster, known as the first non-coding oncogene and referred to as oncomir-1, has been found commonly amplified in many types of malignancies including B-cell lymphoma, T-cell lymphoma, colorectal cancer, breast cancer, hepatocellular carcinoma and osteosarcoma [18–23]. The miRNAs contained in this cluster promotes cell proliferation and suppress cell apoptosis through various pathways [24]. They also function as mediators of angiogenesis that induced by the oncogene c-Myc in tumors [25]. On the other hand, the let-7 family of miRNAs was among the first identified miRNAs that suppress the expression of oncogenes and act as tumor suppressors. In lung cancer cells, let-7 inhibits the proto-oncogene Ras expression and its down-regulation correlates significantly with a poor patient prognosis [26].

Now we know that there is a global decrease in miRNA expression in tumor tissues comparing with their corresponding normal tissues, reflecting a degree of less cell differentiation [5,27]. In addition to this general trend, certain miRNAs function as master regulators, either as oncogenes or tumor suppressors, in cancer progression. Many of these miRNAs also play a role beyond the tumor-initiating process and directly regulate tumor metastasis [28–30], through both changing the intrinsic properties of cancer cells and shaping the interactions between cancer cells and other components of the tumor microenvironment [31]. Differing from protein coding genes, the exact function of a given

miRNA is highly dependent on the cellular context, such as the relative expression of target genes present in the cell and the level of certain RNA-binding proteins that regulate miRNA-target interactions. This characterization of miRNAs provides a possibility that, through analyzing the gene expression pattern of a specific patient, miRNAs may serve as patient “tailored” diagnostic markers or anti-cancer agents and provide a toolbox in personalized treatment of cancer patients.

2 MTA family members in cancer progression

Metastasis-associated proteins (MTAs, or metastatic tumor antigens) are a small protein family encoded by three distinct genes in human genome [32,33]. The founding member of this protein family, MTA1, was first identified in 1994 through a differential cDNA library screening comparing mRNA expression levels in rat mammary adenocarcinoma cell lines with different metastatic abilities [34]. MTA1 displays a much higher expression level in highly metastatic cells than in non-metastatic cells. The nomenclature of this protein family clearly reflects the origin of their discovery. Although the importance of MTA1 in tumor progression was recognized early, its molecular function remains elusive until 1998, when a proteomic study revealed MTA1 as an integral component of the nucleosome remodeling and histone deacetylation (NuRD) complexes [35]. The NuRD complex is a multi-subunit protein complex containing both histone deacetylase and nucleosome-dependent ATPase subunits [36]. In the current understanding of gene regulation, NuRD complex can be recruited into specific gene region through protein-protein interactions or protein-DNA interactions and silence gene transcription by deacetylation of associated histones [37]. Interestingly, several subunits of this complex, particularly the MTA family members, present heterogeneity at the protein level. A hypothesis has been proposed that incorporation of specific subunits into the complex might determine the functional specialization of the complex itself [38]. The three MTA genes in human genome encode at least six protein products (MTA1, MTA1s, MTA1-ZG29p, MTA2, MTA3 and MTA3L) that have non-redundant functions [32]. To date, several studies have been published to support the notion that MTA proteins are able to specify the function of NuRD complexes in the context of cancer [39]. For example, MTA3 has been found to incorporate into the NuRD complex and repress the expression of Snail, a master transcription regulator of epithelial to mesenchymal transition (EMT) and plays an important role in mediating cancer metastasis. However, MTA1 or MTA2 are unable to substitute for MTA3 and regulate Snail expression [40].

As an integral component of the NuRD complex, MTA proteins suppress the expression of a number of tumor suppressor genes and thus contribute to cancer cell transformation and invasion. For example, MTA1 has been reported to transform Rat1 fibroblasts through suppressing Gi2 α expression in a NuRD complex-dependent manner and resulting in a profound stimulation of the Ras pathway [41]. Similarly, MTA1-NuRD complex has also been found to associate with the E-cadherin gene in a specific cell state and suppress its transcription. Since E-cadherin plays an essential role in epithelial cell adhesion, MTA1 thus directly contributes to EMT and cancer cell invasion [42]. Additionally, MTA1 also interacts with ER α and thus represses ER α transcriptional activity through guiding NuRD complex to ER α target genes [43]. It should be noted that MTA-containing NuRD complexes are also capable of deacetylation of non-histone proteins. In the context of

cancer, two well-studied cancer regulators, p53 and HIF1 α , have been found as substrates of NuRD complexes and recognized by different MTA family proteins. The p53 tumor suppressor interacts with MTA2 directly and is significantly deacetylated via this interaction. Deacetylation of p53 marks it for degradation through the MDM2 pathway and results in a decrease of p53-dependent transcription [44]. Differently, HIF1 α interacts with MTA1 and is deacetylated by the MTA1-containing NuRD complex. Deacetylation of HIF1 α actually increases its stability and promotes cell survival in hypoxic conditions [45].

In the past few years, more evidence has emerged on the molecular mechanisms of how MTA family proteins regulate cancer progression. Surprisingly, multiple studies demonstrated that MTA proteins were able to function as a coactivator of gene expression, when not in association with the NuRD complex, and changed the conventional paradigm of MTA function. The first piece of evidence showing the coactivator role of MTA comes from the regulation of breast cancer amplified sequence 3 (BCAS3) gene by MTA1 [46]. In MCF7 cells, MTA1 protein is acetylated at its lysine 626 site and thus obtains the ability to recruit RNA polymerase II complex to the BCAS3 gene promoter. Because of the oncogenic role of BCAS3, MTA1 promotes the malignant phenotypes of this breast tumor cell line through the MTA1-BCAS3 pathway [46]. A similar regulation has been reported in B cells as well. In this case, acetylated MTA1 was directly recruited to the promoter of Pax5, a transcription factor with oncogenic function in B-cell lymphogenesis, and facilitate its expression [47,48]. In addition, more recent studies have connected MTA1 with inflammation [49–51], a process studied in the context of cancer for a long time because persistent inflammation contributes to the initiation and development of cancerous phenotypes [52,53]. By studying the MTA1 expression and function in macrophages, Pakala and colleagues found that MTA1 was a direct target of NF- κ B, the central transcriptional regulator in inflammation response. Moreover, in stimulated macrophages, the association of MTA1 with other NuRD complex subunits was impaired due to unclear reasons; and MTA1 functioned as a coactivator for multiple inflammatory cytokines including IL-1 β and TNF α in this situation [49].

3 MTA family genes regulated by miRNAs

The illustration of distinctive function of different MTA family members and the emergence of evidence showing the bi-regulatory role of MTA proteins as both corepressor and coactivator raise many questions on how to fully understand their biological function in cancer development. For example, with a given number of existing NuRD complexes in a cell, do MTA proteins compete with each other for their incorporation? If this is the case, do relative expression levels of MTA proteins determine which subsets of genes to be repressed? Is acetylation of MTA1 the only factor to determine the switch from corepressor to coactivator? Is there a threshold of MTA1 expression, for example, when the number of MTA1 proteins exceeds the need to form NuRD complexes, to start acetylation and switch to coactivator? To answer these questions, a complete understanding of transcriptional and post-transcriptional regulation of MTA genes is necessary. Recently, several studies suggested a link between certain miRNAs with MTA protein expression levels [54–60]. Given the fact that miRNAs can act as “rheostats” to fine-tune protein expression in subtle

magnitude [61,62], it is intriguing to investigate whether certain miRNAs can function as the mediators to decide the functional mode of MTA proteins.

The first piece of evidence of miRNA regulating MTA family proteins was found in breast cancer cells. In 2009, Reddy et al. reported that miR-661 directly recognizes the 3'UTR of MTA1 mRNA and thus represses MTA1 expression at the protein level [54]. MiR-661 is positively regulated by transcription factor c/EBP α , a tumor suppressor that is frequently down-regulated in breast cancer cells. As a result, down-regulation of c/EBP α in breast cancer cells leads to a decreased miR-661 expression and an enhanced MTA1 protein level. In addition, ectopic expression of miR-661 significantly compromised cancer cell invasion and anchorage-independent growth [54]. Without regulating other MTA family members, miR-661 specifically suppresses MTA1 expression; but it is unclear whether alteration of this miRNA will lead to a re-distribution of NuRD complexes on different genomic regions. Interestingly, the same group found that the miR-661-MTA1 pathway is conserved in hepatocellular carcinoma cells infected by hepatitis B virus (HBV) [55]. In these cells, HBx, a major regulator of cellular responses encoded by HBV, induces MTA1 expression through suppressing miR-661 expression [55]. Additional miRNAs have been found to regulate the expression of MTA1. Using endometrial cancer cells as an experimental system, Zhou et al. reported that miR-30c negatively regulated MTA1 and suppressed cancer cell proliferation and migration [58]. The miR-30c-MTA1 pathway has also been found in non-small cell lung cancer (NSCLC) cells, demonstrating its functional importance in different cancer types [59].

In 2010, Li et al. reported that miR-146a suppressed MTA2 expression in pancreatic cancer cells [56]. MTA2 was among a group of proteins that were simultaneously suppressed by miR-146a and contributed to cell invasion [56]. In addition, miR-34a, a well-studied miRNA in the context of cancer as a direct target of p53 and induces cell cycle arrest [63], has been found to suppress MTA2 at both the mRNA and protein levels [57]. This down-regulation is believed to form a positive feed-back-loop of p53 and miR-34a since MTA2 deacetylated p53 and induced its degradation [57]. Recently, MTA3 has also been found as a direct target of miRNA regulation. In NSCLC cells, miR-495 directly suppresses MTA3 at the protein level and thus compromises cancer cell proliferation and migration [60]. Importantly, a correlation between miR-495 and MTA3 has been observed in a cohort of 56 NSCLC patient tissue samples [60]. As another aspect of the miRNA-MTA relationship, MTA1 has been found to regulate the expression of a group of miRNAs in NSCLC cells [64]. One of these miRNAs, miR-125b, is reported as an important mediator for MTA1 to promote NSCLC cell migration and invasion [65]. However, the mechanism of how MTA1 regulates miRNA expression is still unknown. It is also unclear if miRNA-MTA can form regulatory feedback loops to maintain a bistable state.

The study of miRNAs that regulate MTA family proteins is still in its nascent stage. Although several miRNAs have been validated as *bona fide* regulators of MTA proteins as discussed above, experiments that sophisticatedly designed to test the effects of miRNA-MTA pathway on targets selection of NuRD complexes are still lacking. In addition, given the fact that there are additional naturally occurring MTA variants such as MTA1s, which is generated by alternative splicing of MTA1 gene and mainly functions in the cytoplasm to

sequester ER α [66], it is worthy exploring if certain miRNAs regulate cancer progression through specifically modulating these variants derived from differential splicing events. Moreover, currently it is totally unknown whether miRNAs may play a role in the functional switch of MTA1 protein from acting as a corepressor to acting as a coactivator. Studies intend to answer these questions may provide central pieces of evidence to understand the biological functions of MTA proteins in cancer progression.

4 Concluding Remarks

Since the cloning of MTA1 cDNA in 1994 [34], the past two decades have observed the dramatic expansion of our understanding in the molecular details of MTA family members' functions. Recent studies demonstrating the bi-regulatory nature of MTA1 challenged the conventional paradigm of MTA function and raised many questions in fully understanding their roles in cancer progression. In the meantime, although several reports have identified certain miRNAs as regulators of different MTA family proteins, a complete analysis of the impact of MTA regulating miRNAs at the genome level is still needed. In addition, the effects of MTA regulating miRNAs on the corepressor-coactivator switch remain mysterious. Given the important functions of MTA family proteins in a variety of cancer types, answering these important questions may provide opportunities in the future to develop miRNA-based therapies that benefit cancer patients through modulating the functional status of MTA proteins.

References

1. Eddy SR. Non-coding RNA genes and the modern RNA world. *Nat Rev Genet.* 2001; 2(12):919–929.10.1038/35103511 [PubMed: 11733745]
2. Bartel DP. MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell.* 2004; 116(2):281–297. [PubMed: 14744438]
3. Bushati N, Cohen SM. microRNA functions. *Annu Rev Cell Dev Biol.* 2007; 23:175–205.10.1146/annurev.cellbio.23.090506.123406 [PubMed: 17506695]
4. Calin GA, Croce CM. MicroRNA signatures in human cancers. *Nat Rev Cancer.* 2006; 6(11):857–866.10.1038/nrc1997 [PubMed: 17060945]
5. Lu J, Getz G, Miska EA, Alvarez-Saavedra E, Lamb J, Peck D, et al. MicroRNA expression profiles classify human cancers. *Nature.* 2005; 435(7043):834–838.10.1038/nature03702 [PubMed: 15944708]
6. Sayed D, Abdellatif M. MicroRNAs in development and disease. *Physiol Rev.* 2011; 91(3):827–887.10.1152/physrev.00006.2010 [PubMed: 21742789]
7. Esquela-Kerscher A, Slack FJ. Oncomirs - microRNAs with a role in cancer. *Nat Rev Cancer.* 2006; 6(4):259–269.10.1038/nrc1840 [PubMed: 16557279]
8. Hammond SM. MicroRNAs as tumor suppressors. *Nature Genetics.* 2007; 39(5):582–583. [PubMed: 17460676]
9. Chen CZ. MicroRNAs as oncogenes and tumor suppressors. *New England Journal of Medicine.* 2005; 353(17):1768–1771.10.1056/Nejmp058190 [PubMed: 16251533]
10. Nicoloso MS, Spizzo R, Shimizu M, Rossi S, Calin GA. MicroRNAs--the micro steering wheel of tumour metastases. *Nat Rev Cancer.* 2009; 9(4):293–302.10.1038/nrc2619 [PubMed: 19262572]
11. Ma L, Weinberg RA. Micromanagers of malignancy: role of microRNAs in regulating metastasis. *Trends Genet.* 2008; 24(9):448–456.10.1016/j.tig.2008.06.004 [PubMed: 18674843]
12. Kim VN. MicroRNA biogenesis: coordinated cropping and dicing. *Nat Rev Mol Cell Biol.* 2005; 6(5):376–385.10.1038/nrm1644 [PubMed: 15852042]

13. Bartel DP. MicroRNAs: target recognition and regulatory functions. *Cell*. 2009; 136(2):215–233.10.1016/j.cell.2009.01.002 [PubMed: 19167326]
14. Fabian MR, Sonenberg N. The mechanics of miRNA-mediated gene silencing: a look under the hood of miRISC. *Nat Struct Mol Biol*. 2012; 19(6):586–593.10.1038/nsmb.2296 [PubMed: 22664986]
15. Ameres SL, Zamore PD. Diversifying microRNA sequence and function. *Nat Rev Mol Cell Biol*. 2013; 14(8):475–488.10.1038/nrm3611 [PubMed: 23800994]
16. Calin GA, Sevignani C, Dan Dumitru C, Hyslop T, Noch E, Yendamuri S, et al. Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. *Proceedings of the National Academy of Sciences of the United States of America*. 2004; 101(9):2999–3004.10.1073/Pnas.0307323101 [PubMed: 14973191]
17. Gaur A, Jewell DA, Liang Y, Ridzon D, Moore JH, Chen CF, et al. Characterization of microRNA expression levels and their biological correlates in human cancer cell lines. *Cancer Research*. 2007; 67(6):2456–2468.10.1158/0008-5472.Can-06-2698 [PubMed: 17363563]
18. Connolly E, Melegari M, Landgraf P, Tchaikovskaya T, Tennant BC, Slagle BL, et al. Elevated expression of the miR-17-92 polycistron and miR-21 in hepatitis virus-associated hepatocellular carcinoma contributes to the malignant phenotype. *Am J Pathol*. 2008; 173(3):856–864.10.2353/ajpath.2008.080096 [PubMed: 18688024]
19. Diosdado B, van de Wiel MA, Terhaar Sive Droste JS, Mongera S, Postma C, Meijerink WJ, et al. MiR-17-92 cluster is associated with 13q gain and c-myc expression during colorectal adenoma to adenocarcinoma progression. *Br J Cancer*. 2009; 101(4):707–714.10.1038/sj.bjc.6605037 [PubMed: 19672269]
20. Inomata M, Tagawa H, Guo YM, Kameoka Y, Takahashi N, Sawada K. MicroRNA-17-92 down-regulates expression of distinct targets in different B-cell lymphoma subtypes. *Blood*. 2009; 113(2):396–402.10.1182/blood-2008-07-163907 [PubMed: 18941111]
21. Mavrakis KJ, Wolfe AL, Oricchio E, Palomero T, de Keersmaecker K, McJunkin K, et al. Genome-wide RNA-mediated interference screen identifies miR-19 targets in Notch-induced T-cell acute lymphoblastic leukaemia. *Nat Cell Biol*. 2010; 12(4):372–379.10.1038/ncb2037 [PubMed: 20190740]
22. Huang G, Nishimoto K, Zhou Z, Hughes D, Kleinerman ES. miR-20a encoded by the miR-17-92 cluster increases the metastatic potential of osteosarcoma cells by regulating Fas expression. *Cancer Res*. 2012; 72(4):908–916.10.1158/0008-5472.CAN-11-1460 [PubMed: 22186140]
23. Kim K, Chadalapaka G, Lee SO, Yamada D, Sastre-Garau X, Defossez PA, et al. Identification of oncogenic microRNA-17-92/ZBTB4/specificity protein axis in breast cancer. *Oncogene*. 2012; 31(8):1034–1044.10.1038/ncr.2011.296 [PubMed: 21765466]
24. He L, Thomson JM, Hemann MT, Hernando-Monge E, Mu D, Goodson S, et al. A microRNA polycistron as a potential human oncogene. *Nature*. 2005; 435(7043):828–833.10.1038/Nature03552 [PubMed: 15944707]
25. Dews M, Homayouni A, Yu D, Murphy D, Sevignani C, Wentzel E, et al. Augmentation of tumor angiogenesis by a Myc-activated microRNA cluster. *Nat Genet*. 2006; 38(9):1060–1065.10.1038/ng1855 [PubMed: 16878133]
26. Johnson SM, Grosshans H, Shingara J, Byrom M, Jarvis R, Cheng A, et al. RAS is regulated by the let-7 MicroRNA family. *Cell*. 2005; 120(5):635–647.10.1016/J.Cell.2005.01.014 [PubMed: 15766527]
27. Chang TC, Yu D, Lee YS, Wentzel EA, Arking DE, West KM, et al. Widespread microRNA repression by Myc contributes to tumorigenesis. *Nat Genet*. 2008; 40(1):43–50.10.1038/ng.2007.30 [PubMed: 18066065]
28. Ma L, Teruya-Feldstein J, Weinberg RA. Tumour invasion and metastasis initiated by microRNA-10b in breast cancer. *Nature*. 2007; 449(7163):682–688.10.1038/nature06174 [PubMed: 17898713]
29. Gregory PA, Bert AG, Paterson EL, Barry SC, Tsykin A, Farshid G, et al. The miR-200 family and miR-205 regulate epithelial to mesenchymal transition by targeting ZEB1 and SIP1. *Nat Cell Biol*. 2008; 10(5):593–601.10.1038/ncb1722 [PubMed: 18376396]

30. Tavazoie SF, Alarcon C, Oskarsson T, Padua D, Wang QQ, Bos PD, et al. Endogenous human microRNAs that suppress breast cancer metastasis. *Nature*. 2008; 451(7175):147–U143.10.1038/Nature06487 [PubMed: 18185580]
31. Zhang Y, Yang P, Wang XF. Microenvironmental regulation of cancer metastasis by miRNAs. *Trends Cell Biol*. 2014; 24(3):153–160.10.1016/j.tcb.2013.09.007 [PubMed: 24125906]
32. Manavathi B, Kumar R. Metastasis tumor antigens, an emerging family of multifaceted master coregulators. *Journal of Biological Chemistry*. 2007; 282(3):1529–1533.10.1074/jbc.R600029200 [PubMed: 17142453]
33. Toh Y, Nicolson GL. The role of the MTA family and their encoded proteins in human cancers: molecular functions and clinical implications. *Clinical & Experimental Metastasis*. 2009; 26(3): 215–227.10.1007/s10585-008-9233-8 [PubMed: 19116762]
34. 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. *Journal of Biological Chemistry*. 1994; 269(37):22958–22963. [PubMed: 8083195]
35. Xue YT, Wong JM, Moreno GT, Young MK, Cote J, Wang WD. NURD, a novel complex with both ATP-dependent chromatin-remodeling and histone deacetylase activities. *Molecular Cell*. 1998; 2(6):851–861.10.1016/s1097-2765(00)80299-3 [PubMed: 9885572]
36. Ng HH, Bird A. Histone deacetylases: silencers for hire. *Trends Biochem Sci*. 2000; 25(3):121–126. [PubMed: 10694882]
37. Denslow SA, Wade PA. The human Mi-2/NuRD complex and gene regulation. *Oncogene*. 2007; 26(37):5433–5438.10.1038/sj.onc.1210611 [PubMed: 17694084]
38. Bowen NJ, Fujita N, Kajita M, Wade PA. Mi-2/NuRD: multiple complexes for many purposes. *Biochimica Et Biophysica Acta-Genes Structure and Expression*. 2004; 1677(1–3):52–57.10.1016/j.bbaexp.2003.10.010
39. Li DQ, Pakala SB, Nair SS, Eswaran J, Kumar R. Metastasis-associated protein 1/nucleosome remodeling and histone deacetylase complex in cancer. *Cancer Res*. 2012; 72(2):387–394.10.1158/0008-5472.CAN-11-2345 [PubMed: 22253283]
40. Fujita N, Jaye DL, Kajita M, Geigerman C, Moreno CS, Wade PA. MTA3, a Mi-2/NuRD complex subunit, an invasive growth pathway in breast. *Cell*. 2003; 113(2):207–219.10.1016/s0092-8674(03)00234-4 [PubMed: 12705869]
41. Ohshiro K, Rayala SK, Wigerup C, Pakala SB, Natha RS, Gururaj AE, et al. Acetylation-dependent oncogenic activity of metastasis-associated protein 1 co-regulator. *EMBO Rep*. 2010; 11(9):691–697.10.1038/embor.2010.99 [PubMed: 20651739]
42. Pakala SB, Singh K, Reddy SD, Ohshiro K, Li DQ, Mishra L, et al. TGF-beta1 signaling targets metastasis-associated protein 1, a new effector in epithelial cells. *Oncogene*. 2011; 30(19):2230–2241.10.1038/onc.2010.608 [PubMed: 21258411]
43. 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.
44. Luo JY, Su F, Chen DL, Shiloh A, Gu W. Deacetylation of p53 modulates its effect on cell growth and apoptosis. *Nature*. 2000; 408(6810):377–381. [PubMed: 11099047]
45. Yoo YG, Kong G, Lee MO. Metastasis-associated protein 1 enhances stability of hypoxia-inducible factor-1 alpha protein by recruiting histone deacetylase 1. *Embo Journal*. 2006; 25(6): 1231–1241.10.1038/sj.emboj.7601025 [PubMed: 16511565]
46. Gururaj AE, Singh RR, Rayala SK, Holm C, den Hollander P, Zhang H, et al. MTA1, a transcriptional activator of breast cancer amplified sequence 3. *Proceedings of the National Academy of Sciences of the United States of America*. 2006; 103(17):6670–6675.10.1073/pnas.0601989103 [PubMed: 16617102]
47. Balasenthil S, Gururaj AE, Talukder AH, Bagheri-Yarmand R, Arrington T, Haas BJ, et al. Identification of Pax5 as a target of MTA1 in B-cell lymphomas. *Cancer Research*. 2007; 67(15): 7132–7138.10.1158/0008-5472.Can-07-0750 [PubMed: 17671180]
48. Cobaleda C, Schebesta A, Delogu A, Busslinger M. Pax5: the guardian of B cell identity and function. *Nat Immunol*. 2007; 8(5):463–470.10.1038/ni1454 [PubMed: 17440452]

49. 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 Biol Chem.* 2010; 285(31):23590–23597.10.1074/jbc.M110.139469 [PubMed: 20519513]
50. Pakala SB, Reddy SD, Bui-Nguyen TM, Rangparia SS, Bommana A, Kumar R. MTA1 coregulator regulates LPS response via MyD88-dependent signaling. *J Biol Chem.* 2010; 285(43):32787–32792.10.1074/jbc.M110.151340 [PubMed: 20702415]
51. Ghanta KS, Pakala SB, Reddy SD, Li DQ, Nair SS, Kumar R. MTA1 coregulation of transglutaminase 2 expression and function during inflammatory response. *J Biol Chem.* 2011; 286(9):7132–7138.10.1074/jbc.M110.199273 [PubMed: 21156794]
52. Coussens LM, Werb Z. Inflammation and cancer. *Nature.* 2002; 420(6917):860–867.10.1038/nature01322 [PubMed: 12490959]
53. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature.* 2008; 454(7203):436–444.10.1038/nature07205 [PubMed: 18650914]
54. Divijendra S, Reddy N, Pakala SB, Ohshiro K, Rayala SK, Kumar R. MicroRNA-661, a c/EBP alpha Target, Inhibits Metastatic Tumor Antigen 1 and Regulates Its Functions. *Cancer Research.* 2009; 69(14):5639–5642.10.1158/0008-5472.can-09-0898 [PubMed: 19584269]
55. Bui-Nguyen TM, Pakala SB, Sirigiri DR, Martin E, Murad F, Kumar R. Stimulation of inducible nitric oxide by hepatitis B virus transactivator protein HBx requires MTA1 coregulator. *J Biol Chem.* 2010; 285(10):6980–6986.10.1074/jbc.M109.065987 [PubMed: 20022949]
56. Li Y, VandenBoom TG II, Wang Z, Kong D, Ali S, Philip PA, et al. miR-146a Suppresses Invasion of Pancreatic Cancer Cells. *Cancer Research.* 2010; 70(4):1486–1495.10.1158/0008-5472.can-09-2792 [PubMed: 20124483]
57. Kaller M, Liffers S-T, Oeljeklaus S, Kuhlmann K, Roeh S, Hoffmann R, et al. Genome-wide Characterization of miR-34a Induced Changes in Protein and mRNA Expression by a Combined Pulsed SILAC and Microarray Analysis. *Molecular & Cellular Proteomics.* 2011; 10(8):10.1074/mcp.M111.010462
58. Zhou H, Xu X, Xun Q, Yu D, Ling J, Guo F, et al. microRNA-30c negatively regulates endometrial cancer cells by targeting metastasis-associated gene-1. *Oncology Reports.* 2012; 27(3):807–812.10.3892/or.2011.1574 [PubMed: 22139444]
59. Chen Y. Down-regulation of MiR-30c promotes the Invasion of Non-Small Cell Lung Cancer by Targeting MTA1 (vol 32, pg 476, 2013). *Cellular Physiology and Biochemistry.* 2013; 32(4): 1124–1124.10.1159/000354512
60. Chu H, Chen X, Wang H, Du Y, Wang Y, Zang W, et al. MiR-495 regulates proliferation and migration in NSCLC by targeting MTA3. *Tumor Biology.* 2014; 35(4):3487–3494.10.1007/s13277-013-1460-1 [PubMed: 24293376]
61. Baek D, Villen J, Shin C, Camargo FD, Gygi SP, Bartel DP. The impact of microRNAs on protein output. *Nature.* 2008; 455(7209):64–71.10.1038/nature07242 [PubMed: 18668037]
62. Selbach M, Schwanhaussner B, Thierfelder N, Fang Z, Khanin R, Rajewsky N. Widespread changes in protein synthesis induced by microRNAs. *Nature.* 2008; 455(7209):58–63.10.1038/nature07228 [PubMed: 18668040]
63. He L, He X, Lim LP, de Stanchina E, Xuan Z, Liang Y, et al. A microRNA component of the p53 tumour suppressor network. *Nature.* 2007; 447(7148):1130–1134.10.1038/nature05939 [PubMed: 17554337]
64. Zhu X, Zhang X, Wang H, Song Q, Zhang G, Yang L, et al. MTA1 gene silencing inhibits invasion and alters the microRNA expression profile of human lung cancer cells. *Oncology Reports.* 2012; 28(1):218–224.10.3892/or.2012.1770 [PubMed: 22576802]
65. Li Y, Chao Y, Fang Y, Wang J, Wang M, Zhang H, et al. MTA1 promotes the invasion and migration of non-small cell lung cancer cells by downregulating miR-125b. *Journal of Experimental & Clinical Cancer Research.* 2013; 3210.1186/1756-9966-32-33
66. Kumar R, Wang RA, Mazumdar A, Talukder AH, Mandal M, Yang ZB, et al. A naturally occurring MTA1 variant sequesters oestrogen receptor-alpha in the cytoplasm. *Nature.* 2002; 418(6898):654–657.10.1038/nature00889 [PubMed: 12167865]

Table 1

List of miRNAs that regulate MTA family members

Direct Target	miRNA	Cancer Type	References
MTA1	miR-661	breast cancer	[54]
	miR-661	hepatocellular carcinoma	[55]
	miR-30c	endometrial cancer	[58]
	miR-30c	non-small cell lung cancer	[59]
MTA2	miR-146a	pancreatic cancer	[56]
	miR-34a	colorectal cancer	[57]
MTA3	miR-495	non-small cell lung cancer	[60]