Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL AT INIST-CNRS

Deep Insight Section

MTA1 of the MTA (metastasis-associated) gene family and its encoded proteins: molecular and regulatory functions and role in human cancer progression

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Published in Atlas Database: June 2010

Online updated version : http://AtlasGeneticsOncology.org/Deep/MTAinCancerID20088.html
DOI: 10.4267/2042/44992

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Abstract

MTA1(a metastasis-associated gene) is a newly discovered human gene (residing on chromsome 14q32.3) that belongs to a family of cancer progression-related genes (*MTA*). The mRNA product of *MTA1*along with its protein product MTA1 have been reported to be over-expressed in a wide variety of animal and human tumors. For example, the expression of *MTA1* and its encoded protein MTA1 correlates with the malignant properties of many human cancers, including cancers of the breast, colon, stomach, liver, prostate and others. The MTA proteins have been shown to be ubiquitinated transcriptional co-repressors that function in histone deacetylation and are part of the NuRD complex, a nucleosome remodeling and histone deacetylating complex whose stability appears to be regulated by ubiquitinated MTA1 binding to E3 ubiquitin ligase constitutive photomorphogenesis protein-1 (COP1). The MTA1 protein plays an essential role in c-MYC-mediated cell transformation, and its expression correlates with mammary gland tumor formation. In the latter, MTA1 helps convert mammary cells to more aggressive phenotypes by repression of the estrogen receptor (ER) via trans-activation through deacetylation of chromatin in the ER-responsive element of ER-responsive genes. Another member of the MTA family, MTA3, is induced by estrogen and represses the expression of the transcriptional repressor Snail, a master regulator of epithelial to mesenchymal transformation, resulting in the expression of the cell adhesion molecule E-cadherinand maintenance of a differentiated, normal epithelial phenotype in mammary cells. An important activity mediated by both MTA1 and MTA2 is deacylation and inactivation of tumor suppressor p53protein, in part by controlling its stability by inhibiting ubiquitination, leading to inhibition of growth arrest and apoptosis. Another factor deacetylated and stabilized by MTA1 NuRD complex is hypoxia-inducible factor-1α (HIF-1α), which is involved in angiogenesis. Therefore, the MTA proteins represent a possible set of master co-regulatory molecules involved in the carcinogenesis and progression of various malignant tumors. As such, they could be important new tools for cancer diagnosis and treatment.

1. Introduction - The MTA gene family

An important advance in cancer research has been the discovery of a wide variety of new molecules involved in carcinogenesis and cancer progression. Although additional cancer-related molecules will be identified in the future, these molecules must fulfill two major requirements in order to be clinically useful as molecular targets useful for the diagnosis and treatment of human cancers (Toh and Nicolson, 2009).

The first is that abnormalities must occur in the expression or structure of the molecules of interest, and their clinical relevance must be definitely demonstrated in independent studies on human cancers. The second is that the underlying molecular mechanisms necessary

for the molecules to exert their functions in carcinogenesis or cancer progression must be determined and confirmed in animal tumor models and clinical specimens.

There have been a number of cancer-related genes and molecules that have been discovered in the last few years. In our laboratory we identified a candidate metastasis-associated gene by the use of a differential cDNA screening method. Using this approach we identified a gene that was differentially over-expressed in highly metastatic rat mammary adenocarcinoma cell lines compared to poorly metastatic lines (Toh et al., 1994; Toh et al., 1995). When this gene was sequenced, it was shown to be a completely new, novel gene without any homologous or related genes in the database at the time. This gene was named *mta1* (metastasis-associated gene-1). A homologous gene was also expressed in human cancer cell lines, and its human cDNA counterpart, *MTA1,* was subsequently cloned (Nawa et al., 2000) and found to reside on chromosome 14q32.3 (Cui et al., 2001).

Using surgically removed human tissues we showed that high levels of *MTA1*mRNA expression were correlated to the invasive and growth properties of gastrointestinal cancers, including esophageal, gastric and colorectal cancers (Toh et al., 1997; Toh et al., 1999). After these studies, several reports from other groups found similar correlations between *MTA1* expression and the malignant potentials of human cancers (reviewed in Toh and Nicolson, 2009).

In addition to *MTA1*, other genes related to *MTA1* have now been identified. This gene family, which we termed the *MTA*family, now has several members plus some splice variants (Toh and Nicolson, 2003; Manavathi and Kumar, 2007; Toh and Nicolson, 2009). Furthermore, studies on the molecular biological and biochemical properties of the MTA family have shown that the gene products of the main members of the family (proteins MTA1, MTA2 and MTA3) are tightly associated in a protein complex called NuRD (nucleosome remodeling and histone deacetylation), which has transcriptional regulatory functions via histone deacetylation and chromatin remodeling (Toh et al., 2000; Bowen et al., 2004). Interestingly, histone deacetylase activities correlate with squamous cell carcinoma invasion (Toh et al., 2003). At the moment, the MTA family has attracted widespread attention as one of several key molecules that play indispensable roles in the pathogenesis and progression of a wide variety of cancers (Toh and Nicolson, 2003; Kumar et al., 2003; Manavathi et al., 2007b; Toh and Nicolson, 2009). We will examine the significance of the expression of MTA family members in human cancers and the important molecular mechanisms that are currently known by which MTA proteins exert their cellular actions as well as discuss the potential clinical applications of this protein family for the diagnosis and treatment of human cancers.

2. The MTA family of proteins, their structures and cell location

The MTA proteins represent a family of gene products encoded by three distinct genes (MTA1, MTA2 and MTA3), and six reported isoforms (MTA1, MTA1s, MTA1-ZG29p, MTA2, MTA3, and MTA3L). The molecular masses of the gene products of MTA1, MTA2 and MTA3 are approximately 80 kDa, 70 kDa and 65 kDa, respectively (Manavathi and Kumar, 2007; Toh and Nicolson, 2009). The nucleotide and protein alignment homologies and the phylogenetic comparative analyses have been discussed previously (Bowen et al., 2004; Manavathi and Kumar, 2007; Toh and Nicolson, 2009).

The MTA gene family sequences, with the exception of ZG-29p, contain several common domain structures (Singh and Kumar, 2007; Toh and Nicolson, 2009). One of these, the BAH (bromo-adjacent homology) domain is involved in protein-protein interactions. Another, the SANT (SWI, ADA2, N-CoR, TFIIIB-B) domain shares a high degree of homology with the DNA-binding domain of the Myb-related proteins, suggesting that this domain may be involved in DNA-binding. The ELM (egl-27 and MTA1 homology) domain has an unknown function but could be involved in embryonic patterning (Solari et al., 1999).

The MTA family members contain a highly conserved GATA-type zinc finger motif, suggesting direct interactions with DNA (Nawa et al., 2000). The MTA1 protein has two src-homology (SH)-binding motifs at its C-terminal end-such binding domains are known to be important in signal transduction involving kinase, adaptor and scaffolding proteins (Toh et al., 1994; Toh et al., 1995; Singh and Kumar, 2007). Similarly, SH2- and SH3-binding domains are also found in MTA2 and MTA3 protein sequences (Toh et al., 1994; Toh et al., 1995; Singh and Kumar, 2007). These common domain structures demonstrate that the MTA family is involved in protein-protein and protein-DNA interactions, indicating the anticipated roles of the MTA family of proteins in signal transduction and transcriptional regulation (Toh and Nicolson, 2003; Singh and Kumar, 2007; Toh and Nicolson, 2009).

In addition to protein-protein and protein-DNA binding, MTA proteins contain basic nuclear localization signals (Toh et al., 1994; Toh et al., 1995; Singh and Kumar, 2007). They also localize in the nucleus in many human cancer cells (Toh et al.,1997; Toh et al., 1999); however, MTA1 localizes to both the cytoplasm and nucleus in some tumors (Moon et al., 2004; Balasenthil et al., 2006; Bagheri-Yarmand et al., 2007). MTA3 also localizes to the nucleus, but without any apparent nuclear localization signal (Fujita et al., 2003). A short splice-variant of MTA1, called MTA1s, is predominantly localized in the cytoplasm (Kumar et al., 2002).

3. MTA protein expression in various cancers and its possible clinical relevance

Since the report by Toh et al. (1997) that the over-expression of *MTA1*was significantly correlated to the malignant properties of human gastric and colorectal cancers, there have been several reports on the expression levels of MTA family members, especially of MTA1, in various human cancers (reviewed in Toh and Nicolson, 2009). These studies revealed that the expression levels of MTA family members correlate with pathogenic significance and prognosis (Toh and Nicolson, 2009). The biological relevance of MTA proteins to carcinogenesis and cancer progression has been investigated in a few cancer models, such as breast and gastrointestinal cancers, and these will be discussed in more detail below.

3.1 MTA1 protein and breast cancer

MTA1 protein was originally identified as a candidate cancer progression molecule that was associated with breast cancer metastasis (Toh et al., 1994; Toh et al., 1995). Subsequently, using antisense RNA of *MTA1* a role for MTA1 in the growth properties of metastatic breast cancer cells was investigated. Using *MTA1*antisense RNA we found that the growth rates of highly metastatic breast cancer cell lines were inhibited significantly in a dose-dependent manner (Nawa et al., 2000). More direct evidence to demonstrate an association of MTA1 expression levels with breast cancer malignant properties was obtained by Mazumdar et al. (2001). They demonstrated that forced expression of the MTA1 protein in the human breast cancer cell line MCF-7 was accompanied by an enhancement in the ability of MCF-7 cells to invade an artificial matrix and ability to grow in an anchorage-independent manner. They also showed that the enhancement was associated with the interaction between MTA1 protein and histone deacetylase, resulting in a repression of estrogen receptor (ER) mediated transcription (Mazumdar et al., 2001).

Using an animal model the Mazumdar et al. (2001) study was extended by further experiments demonstrating a direct in vivo effect of MTA1 on the carcinogenesis of breast cancer cells (Bagheri-Yarmand et al., 2004; Singh and Kumar, 2007). This group established a transgenic mice system that over-expressed the MTA1 protein, and these *MTA1*-transgenic mice revealed inappropriate development of their mammary glands. The *MTA1*-transgenic mice eventually developed hyperplastic nodules and mammary tumors, including mammary adenocarcinomas and lymphomas.

The involvement of MTA1 in the carcinogenesis and progression of breast cancers was also shown by Martin et al. (2001; 2006). First, they mapped the chromosomal locus in 14q that might be responsible for axillary lymph node metastases in human breast cancers by comparing the rate of loss of heterozygosity between node-positive and node-negative breast cancers. The *MTA1* gene was found to be contained in the same gene locus, suggesting that *MTA1*is a candidate for a breast cancer metastasis-promoting gene. Next, using immunohistochemistry they examined MTA1 protein expression in primary human breast cancer samples and demonstrated that node-negative breast cancers with over-expression of MTA1 protein had a higher risk of disease relapse similar to node-positive tumors. Therefore, the over-expression of MTA1 was proposed as a potential predictor of early disease relapse independent of node status (Martin et al,. 2006).

Using surgically resected human breast cancer specimens Jang et al. (2006) showed that MTA1 over-expression was closely associated with higher tumor grade and high intratumoral microvessel density. This suggested that MTA1 could be a useful predictor of an aggressive phenotype, and the MTA1 molecule could be considered as a possible angiogenesis-promoting molecule in breast cancers (Jang et al., 2006).

3.2 MTA1 protein and gastrointestinal cancers

MTA1 over-expression has been shown to be pathogenically significant in human gastrointestinal cancers. Using a reverse-transcription polymerase chain reaction (RT-PCR) method on surgically resected human gastric and colorectal cancer specimens were compared to paired normal counterpart tissues, and we found that the higher expression of *MTA1* mRNA was significantly correlated to the depth of cancer invasion and extent of lymph node metastasis (Toh et al., 1997). This study was the first to demonstrate the clinical relevance of MTA1 expression to the malignant potentials of human cancers. Over-expression of *MTA1* mRNA was also shown in colorectal cancers compared to the normal counterpart tissues (Giannini et al., 2005).

Esophageal cancers have also been investigated for *MTA1*/MTA1 over-expression. Using a RT-PCR method we found that human esophageal squamous cell cancers over-express *MTA1*mRNA (Toh et al., 1999). The over-expressing cancer cells showed significantly higher frequencies of adventitial invasion and lymph node metastasis and tended to have higher rates of lymphatic involvement (Toh et al., 1999). Using immunohistochemistry we further examined the expression levels of MTA1 protein in human esophageal squamous cell cancers and reconfirmed the results obtained by RT-PCR (Toh et al., 2004). In the same study we also demonstrated that MTA1 protein was a predictor of poor prognosis after surgery (Toh et al., 2004).

The roles of *MTA1*/MTA1 in small intestinal cancers have also been evaluated. Kidd et al. (2006a; 2007) and Modlin et al. (2006b) showed that it was useful to examine the expression of *MTA1*mRNA and MTA1 protein in order to determine the malignant potential

and the propensity to metastasize of enterochromaffin cell cancers (small intestinal carcinoid tumors). When compared to nonmetastatic primary tumors, the expression of *MTA1* was increased in malignant, invasive small intestinal carcinoid tumors and in metastases to liver and lymph nodes. In these cells loss of TGFβ expression modified expression, including increased *MTA1* expression, of the genes involved in malignant behavior (Kidd et al., 2007). It was further reported that *MTA1*was a good candidate genetic molecular marker to discriminate between gastric carcinoids and other gastric neoplasms (Kidd et al., 2006b) as well as malignant appendiceal carcinoids from benign tissue (Modlin et al., 2006a). In these studies, *MTA1* and MTA1 expression were thought to be good markers of the malignant potential of carcinoid tumors.

Other gastrointestinal-linked cancers, such as a pancreatic cancers and hepatocellular carcinomas, have also been examined for the involvement of *MTA1*/MTA1 over-expression in carcinogenesis and cancer progression. Iguchi et al. (2000) examined *MTA1* mRNA expression in pancreatic cancer cell lines and resected pancreatic cancer tissues and found that increased levels of *MTA1* mRNA expression in the more progressed pancreatic cancers. Direct evidence on the role of *MTA1*/MTA1 in the progression of pancreatic cancer was provided by Hofer et al. (2004). Using a pancreatic cell line (PANC-1) they transfected *MTA1*cDNA into the cells and found that enhanced expression of MTA1 promoted the acquisition of an invasive and metastatic phenotype and enhanced the malignant potentials of the transformed cells (pancreatic adenocarcinomas) by modulation of the cytoskeleton via IQGAP1. In addition, Miyake et al. (2008) showed the expression level of the MTA1 protein correlated with poorer prognosis of pancreatic cancer patients.

An association between *MTA1*/MTA1 expression and the malignant properties of hepatocellular carcinomas (HCC) was first reported by Hamatsu et al. (2003). In this study, *MTA1* mRNA level was assessed by RT-PCR in resected human HCC tissues, and its high expression predicted a lower disease-free survival rate after curative HCC hepatectomy. Using immunohistochemistry Moon et al. (2004) examined MTA1 protein expression in resected human HCC specimens and found that over-expression of MTA1 was associated with HCC growth and vascular invasion and that nuclear localization of ERa inversely correlated with MTA1 expression. This suggested that MTA1 was involved in negative regulatory mechanisms.

Recently, Yoo et al. (2008) demonstrated that hepatitis B virus (HBV) X (HBx) protein strongly induced the expression of MTA1 and histone deacetylase 1 (HDAC1). This suggests that positive crosstalk between HBx and MTA1/HDAC1 complex may occur, and this could be important in stabilizing hypoxia-inducible factor-1α (HIF1-1α), which appears to play a critical role in angiogenesis and metastasis of HBV-associated HCC (Yoo et al., 2008). Interestingly, it was reported that MTA1 was closely associated with microvascular invasion, frequent postoperative recurrence, and poor prognosis in patients with HCC, especially in those with HBV-associated HCC (Ryu et al., 2008).

3.3 MTA1 protein and other cancers

The reports on *MTA1*/MTA1 over-expression in human cancers have been reinforced by the experimental over-expression or under-expression of MTA1 in human cells. For example, Mahoney et al. (2002) transfected *MTA1* cDNA into immortalized human keratinocytes and demonstrated that forced over-expression of *MTA1*contributed to some metastatic cell properties, such as increased cell migration, invasion and survival in an anchorage independent medium. Nawa et al. (2000) used antisense *MTA1* to suppress MTA1 levels and inhibit the growth of breast cancer cells in vitro. These authors subsequently showed that in vitro invasion of human MBA-MB-231 cells could be inhibited by antisense *MTA1* (Nicolson et al., 2003). Similarly, using a human esophageal squamous cell carcinoma cell line, Qian et al. (2005) inhibited *MTA1* expression by RNA interference and found significant inhibition of the cells' in vitro invasion and migration properties.

Possible relationships between *MTA1*/MTA1 expression and malignant cell properties, such as invasion and metastasis, have been investigated in other carcinoma and sarcoma systems. Using human non-small cell lung cancer cells high expression of *MTA1* mRNA was correlated with lymph node metastasis (Sasaki et al., 2002). This has also been found to be the case in human ovarian cancers (Yi et al., 2003). Additionally, in thymomas advanced stage and invasiveness was related to *MTA1* expression (Sasaki et al., 2001).

Using various techniques the relationship between MTA1 expression and malignancy has been investigated in various cancers. For example, a potential role for MTA1 protein over-expression in the progression of human endometrial carcinomashas been found by Balasenthil et al. (2006). Whereas in prostate cancers Hofer et al. (2004) showed that metastatic prostate tumors had significantly higher levels of MTA1 protein expression and higher percentages of tissue cores staining positive for MTA1 protein over-expression than in clinically localized prostate cancers or benign prostate lesions. Most interestingly, using transgenic mice Kumar's group showed that MTA1 over-expression was accompanied by a high incidence of spontaneous B cell lymphomas, including diffuse large B cell lymphomas (Bagheri-Yarmand et al., 2007; Balasenthil et al., 2007). The high expression of MTA1

in human diffuse B-cell lymphomashas been reported (Hofer et al., 2006). In the transgene model, mammary adenocarcinomas also developed (Bagheri-Yarmand et al., 2004).

Microarrays have also been used to follow *MTA1*and other genes' expression. Using DNA microarray analysis Roepman et al. (2006) investigated gene expression patterns in lymph node metastases of head and neck squamous cell carcinomas. They found that the *MTA1* gene was the only single gene that showed consistent over-expression between large numbers of matched paired samples of primary tumor and lymph node metastases.

4. Biological significance of the MTA proteins

It has been demonstrated by different laboratories (see Section 3) that *MTA1*/MTA1 over-expression is closely correlated with cancer progression (and in some cases with carcinogenesis) in a wide range of different cancers. This strongly indicates that the MTA1 protein may be an important functional molecule in malignancy. Thus, it is necessary to clarify the molecular mechanisms by which the MTA protein family members exert their functions.

Only then can MTA proteins be utilized for diagnosis or treatment of human cancers. There are several important cellular functions of MTA proteins that have been recently clarified, such as those that are related to carcinogenesis and cancer progression.

4.1 MTA proteins and the nucleosome remodeling-histone deacetylation (NuRD) complex and transcriptional regulation

The molecular and biochemical functions of the MTA1 protein were first investigated by four independent groups. In these studies, two different chromatin-modifying activities, ATP-dependent nucleosome remodeling activity and histone deacetylation, were functionally and physically linked in the same protein complex. This complex has been named the NuRD (Nucleosome Remodeling and Histone Deacetylation). The NuRD complex contains HDAC1, HDAC2, the histone binding proteins RbAp46/48 and the dermatomyositis-specific autoantigen Mi-2, which has been shown to have transcription repressing activity (Tong et al., 1998; Xue et al., 1998; Wade et al., 1999; Zhang et al., 1999; Bowen et al., 2004).

The MTA1 protein was found in the NuRD complex by Xue et al. (1998), and this complex also possessed strong transcription repressing activity. Subsequently, Zhang et al. (1999) reported that a protein similar to MTA1 (named the MTA2 protein) was also a component of the NuRD complex, and they found that MTA2 protein was highly expressed in rapidly dividing cells. Later, MTA3 protein was identified as an estrogen-inducible gene product that is present in a distinct NuRD complex (Fujita et al., 2003). We also reported the physical interaction between MTA1 protein and HDAC1 (Toh et al., 2000).

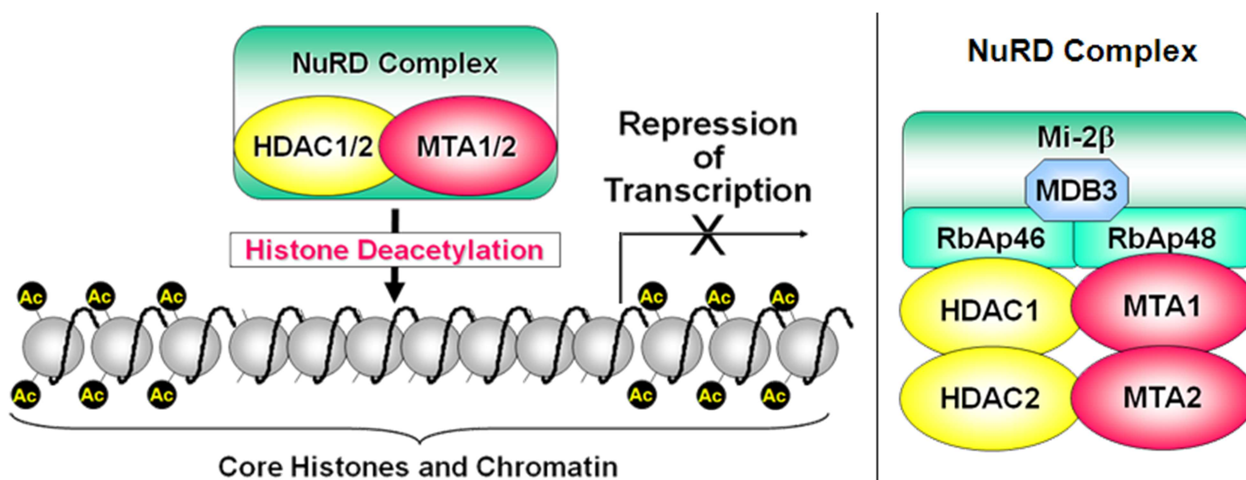

Figure 1. MTA proteins in a chromatin remodeling and histone deacetylation complex (NuRD). This complex has transcription repression properties. The NuRD complex also contains histone deacetylases (HDAC1 and 2), major DNA binding protein 3 (MDB3), histone binding proteins RbAp46/48 and the dermatomyositis-specific autoantigen Mi-2 (from Toh and Nicolson, 2009 with permission).

The basic functions of the MTA protein family members appear to be exerted through NuRD complexes as chromatin remodeling and histone deacetylating activities (Figure 1). Although there are also non-histone deacetylating proteins in NuRD complexes, MTA proteins appear to be among the principal components (Figure 1). In addition, the MTA-NuRD complexes show transcriptional repression activities (Feron, 2003; Kumar et al., 2003; Manavathi et al., 2007b; Singh and Kumar, 2007). Although all MTA protein family members are found in NuRD complexes, each MTA protein may form a distinct NuRD complex that targets different sets of promoters (Bowen et al., 2004).

4.2 MTA protein repression of the trans-activating activity of estrogen receptor-alpha

The involvement of MTA proteins in NuRD complexes suggested that such complexes might function in chromatin remodeling and histone deacetylation, but a direct target of a MTA protein had to first be identified (Mazumdar et al., 2001). MTA1 protein was identified as a molecule induced by heregulin-beta1 (HRG), a growth factor that is a natural ligand of the human epidermal growth factor receptors HER3 and HER4. It can also trans-activate HER2 (c-erbB-2) in human breast cancer cell lines. Mazumdar et al. (2001) showed that MTA1 protein directly interacted with the ligand-binding domain of the estrogen receptor ERα and that HRG stimulated the association of MTA1 and HDAC2 on the chromatin site of an ER-responsive element (ERE) in the promoter regions of estrogen responsive genes, such as pS2 and c-myc. This could explain the activation of the HRG/HER2 pathway in ER-positive breast cancers and the suppression of ERα functions, which could result in the more invasive and aggressive phenotypes observed in ER-negative breast cancers (Cui et al., 2006).

The repressive function of MTA1 protein on ERα is mediated via histone deacetylation by HDAC1 and HDAC2, suggesting that MTA1 protien has a potent co-repressor function during the trans-activation of ERα through histone deacetylation (Figures 2 and 3). MTA2 protein has also been shown to physically interact with ERα and to repress its trans-activating function. This could explain the over-expression of MTA2 protein in cells that were unresponsive to estrogen as well as suppression of estrogen-induced colony formation in breast cancer cells (Cui et al., 2006).

MTA proteins also have other activities. For example, Khaleque et al. (2008) showed that MTA1 protien binds to a heat shock factor 1 (HSF1), the transcriptional activator of the heat shock genes, in vitro and in human breast carcinoma samples. They demonstrated that HSF1-MTA1 complex formation was strongly induced by HRG and that the complex was incorporated into a NuRD complex that participated in the repression of estrogen-dependent transcription in breast cancer cells treated with HRG (Khaleque et al., 2008).

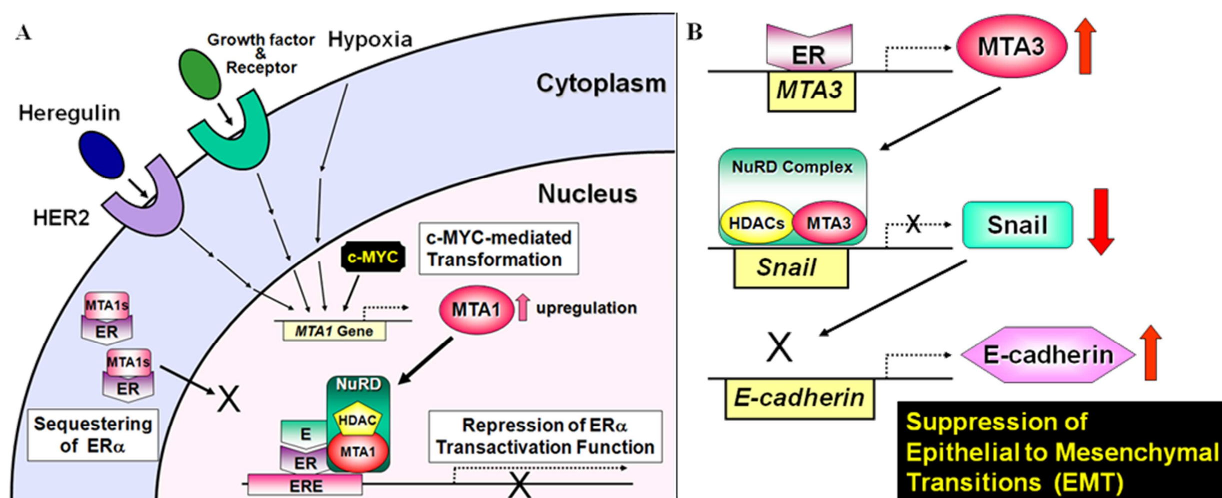

Figure 2. A possible role for MTA proteins in carcinogenesis and cancer progression. In this scheme the main functions of the MTA family of proteins are presented. (**A**) MTA1 protein is included in a NuRD complex that represses the transactivation function of estrogen receptor (ER), rendering breast cancer cells more phenotypically aggressive. MTA1 proteins in NuRD complexes are proposed to be one of the first downstream targets of c-MYC function, and it is essential for the transformation potential of c-MYC. MTA1s is a splice-variant of MTA1 that localizes in the cytoplasm where it sequesters ERα, preventing the ligand-induced nuclear translocation of Erα, thus stimulating the development of the malignant phenotype of breast cancer cells. (**B**) MTA3 protein induced by estrogen represses the expression of the transcriptional repressor Snail, a master regulator of epithelial to mesenchymal transitions, resulting in the expression of the cell adhesion molecule E-cadherin and maintenance of a differentiated, normal epithelial status in breast cells (from Toh and Nicolson, 2009 with permission).

There are apparently several molecules, such as ménage-à-trois 1 (MAT1), MTA1-interacting co-activator (MICoA) and nuclear receptor interacting factor 3 (NRIF3), that can interact with MTA1 protein and repress the trans-activation function of ERα (Manavathi et al., 2007b). These three MTA1-binding proteins themselves have co-activator properties upon ERα trans-activation. MAT1, an assembly and targeting ring finger factor for cyclin-dependent kinase-activating kinase (CAK), has been identified by Talukder et al. (2003) as a MTA1-binding protein. The interactions between CAK and MTA1 protein apparently regulate the trans-activation activity of ERα in a CAK-dependent manner in breast cancer cells. In contrast, MICoA-mediated ERα trans-activation functions are opposed by MTA1 protein through the recruitment of HDACs (Mishra et al., 2003). In addition, the interactions between MTA1 protein and NRIF3 (an estrogen-inducible gene) may be important in modulating the sensitivity of breast cancer cells to estrogen (Talukder et al., 2004).

Another MTA1-binding protein partner, Lim-only protein 4 (LMO4), has been identified by Singh et al. (2005). LMO4 was found to be a component of the MTA1 co-repressor complex, and its over-expression repressed ERα trans-activation in a HDAC-dependent manner. This has been proposed to result in the acquisition of an ERα-negative phenotype with its known increased aggressiveness in breast cancer cells (Singh et al., 2005).

Variants of MTA1 protein have also been found. For example, a truncated form of MTA1 protein has been identified and named MTA1s (Balasenthil et al., 2006). MTA1s is a splice-variant of MTA1, and it contains an ER-binding motif (nuclear binding motif) without any nuclear localization signals at its C-terminus. This truncated MTA protein localizes in the cytoplasm where it sequesters ERα, resulting in the blockage of ERα ligand-induced nuclear translocation and stimulation of acquisition of the malignant phenotype of breast cancer cells. This suggests that the regulation of the cellular localization of ERα by MTA1s protein may represent a mechanism for redirecting nuclear receptor signaling by nuclear exclusion. MTA1s protein has also been shown to associate with casein kinase I-gamma2, which is an estrogen-responsive kinase (Mishra et al., 2004).

MTA3 protein is the newest addition to the MTA family. It was identified as an estrogen-dependent component of the Mi-2/NuRD transcriptional co-repressor complex in breast epithelial cells (Fujita et al., 2003).

The absence of MTA3 protein as well as the absence of ER results in an aberrantly increased expression of the transcriptional repressor Snail, a master regulator of epithelial-to-mesenchymal transition (EMT). This increased expression of Snail results in reduction in expression of the cell adhesion molecule E-cadherin, which subsequently modifies epithelial cell architecture and enhances invasive growth. MTA3 protein is a transcriptional target of ERα, and in the presence of estrogen ERα directly binds to the *MTA3* promoter at the SP1 site in close proximity to the ERE half-site, resulting in stimulation of *MTA3* transcription (Fujita et al., 2004; Mishra et al., 2004). Thus, MTA3 protein may function to maintain a well-differentiated, normal epithelial phenotype in breast cells. This is in stark contrast to MTA1 or MTA1s protein, where up-regulation of MTA1 or MTA1s protein in breast cancer cells may repress *MTA3* expression through repression of the ERα function, resulting in up-regulation of Snail, down-regulation of E-cadherin, promotion of an EMT phenotype and potentially an increase in metastatic potential.

Forced expression of MTA3 protein inhibits ductal branching in virgin and pregnant mammary glands in *MTA3*-transgenic mice (Zhang et al., 2006). This property is in marked contrast to *MTA1*-transgenic mice, where there is inappropriate development of mammary glands, resulting in the development of hyperplastic nodules and mammary tumors, including adenocarcinomas and lymphomas (Bagheri-Yarmand et al., 2004; Manavathi and Kumar, 2007). MTA3 protein also represses Wnt4 transcription and secretion by inhibiting Wnt-target genes in mammary epithelial cells. This repression of Wnt4 transcription was found to be mediated through a MTA3-NuRD complex, which interacts with the Wnt4-containing chromatin in an HDAC-dependent process (Zhang et al., 2006).

The fundamental actions of the MTA proteins are exerted via transcriptional repression by histone deacetylation; however, a transcriptional activating function has also been described for MTA complexes. Gururaj et al. (2006a, 2006b) showed that breast cancer amplified sequence 3 (BCAS3), a gene amplified and over-expressed in breast cancers, was a chromatin target of MTA1 protein, and the transcription of BCAS3 was stimulated by MTA1 protein. This suggested that MTA1 protein has a transcriptional co-activator function in addition to its co-repressor function. A similar property has been also been suggested for mouse Mta2 protein (Matsusue et al., 2001).

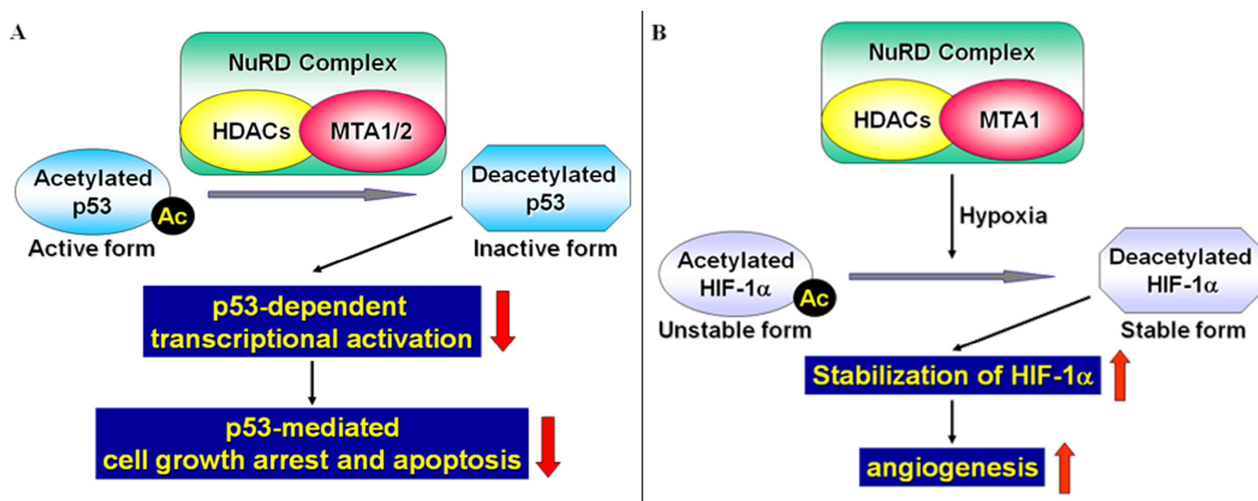

Figure 3. Deacetylation of non-histone proteins by MTA protein family complexes. (**A**) Tumor suppressor p53 protein is deacetylated and inactivated by both MTA1 and MTA2 proteins in NuRD complexes, resulting in inhibition of growth arrest and apoptosis. (**B**) Hypoxiainducible factor-1α (HIF-1α) is also deacetylated and stabilized by MTA1 protein, leading to angiogenesis (from Toh and Nicolson, 2009 with permission).

4.3 MTA-NuRD protein complexes and deacetylation of non-histone proteins

Chromatin histones and non-histone proteins are the protein targets for deacetylation by HDAC via NuRD complexes containing MTA proteins. The tumor suppressor gene p53 protein was the first non-histone protein that was reported to be deacetylated by MTA protein-containing NuRD complexes. Luo et al. (2000) reported that the deacetylation of p53 was mediated by an HDAC1 complex containing MTA2 protein. A MTA2-associated NuRD complex was involved, and this HDAC1/MTA2 complex interacted with p53 in vitro and in vivo and reduced significantly the steady-state levels of acetylated p53. Deacetylation of p53 causes an increase in its own degradation through MDM2 and a reduction in p53-dependent transcriptional activation. Eventually this results the repression of the normal p53 function that mediates cell growth arrest and apoptosis (Figure 3). The same phenomenon was observed between p53 and MTA1 complexes. HDAC1/MTA1 complexes possessed deacetylation activity against p53 protein in human non-small cell carcinoma and human hepatoma cells, and the complexes were found to inhibit p53-induced apoptosis by attenuating the trans-activation function of p53 (Moon et al., 2007). More recently the stability of p53 was determined to be affected by MTA1 inhibiting p53 ubiquitination by E3 ubiquitin ligases double minute 2 (Mdm2) and constitutive photomorphogenic protein 1 (COP1). MTA1 competes with COP1 to bind to p53 and/or destabilize COP1 and Mdm2 (Li et al., 2009b). MTA1 stability and degradation itself is controlled by ubiquitination, and degradation of MTA1 is promoted by COP1-mediated hydrolysis (Li et al., 2009b).

HIF-1α (hypoxia-inducible factor-1α) is another important non-histone protein that is deacetylated by HDAC1/MTA1 complexes (Figure 3). HIF-1α is a key regulator of angiogenic factors (Yoo et al., 2006). The expression of MTA1 was strongly induced under hypoxic conditions in breast cancer cell lines, and MTA1 protein over-expression enhanced the transcriptional activity and stability of HIF-1α protein. MTA1 protein physically bound to HIF-1α and deacetylated it by increasing the expression of HDAC1, leading to the stabilization of HIF-1α (Yoo et al., 2006). These results indicated possible positive cross-talk between MTA1 and HIF-1α, mediated by HDAC1 recruitment.

Moon et al. (2006) found a close connection between MTA1-associated metastasis and HIF-1α-induced tumor angiogenesis. They showed that MTA1 protein increased the transcriptional activity of HIF-1α and a target molecule of HIF-1α, vascular endothelial growth factor (VEGF). Conditioned medium collected from *MTA1*-transfectants increased angiogenesis in vitro and in vivo (Moon et al., 2006). Functional links between HIF-1α and MTA1 protein have been demonstrated in clinical samples of pancreatic carcinoma. Using immunohistochemistry and surgically resected pancreatic carcinomas Miyake et al. (2008) examined the expression of HIF-1α, HDAC1 and MTA1 proteins and suggested that HIF-1α expression, which is associated with a poor prognosis in patients with pancreatic cancers, might be regulated by HDAC1/MTA1 complexes. The contribution of MTA1 protein to tumor angiogenesis was also demonstrated in human breast cancers. Using immunohistochemistry Jang et al. (2006) examined MTA1 protein expression and intra-tumoral microvessel density (MVD) in clinical samples of breast cancer and showed that MTA1 protein expression was significantly correlated with higher tumor grade and higher tumor MVD.

The relationship between MTA1 protein expression and MVD was also observed in hepatitis B-associated HCC (Ryu et al., 2008). In this tumor system hepatitis B

virus X protein (Hbx) induces the expression of MTA1 protein and its HDAC1 complex, which enhances hypoxia signaling in HCC (Yoo et al., 2006). This suggests that the HDAC1 complex containing MTA1 protein may be important in stabilizing HIF-1α, and thus play a role in angiogenesis and metastasis.
The relationship between the protein members of NuRD complexes, including MTA1 and MTA2 proteins, and the ataxia teleangiectasia mutated (ATM)- and Rad3-related protein (ATR) has been shown by co-immunoprocipitation of these proteins (Schmidt and Schreiber, 1999). ATR is a phosphatidylinositol-kinase-related kinase that has been implicated in the response of human cells to multiple forms of DNA damage and may play a role in the DNA replication checkpoint. This suggests that MTA proteins may contribute to the regulation of DNA checkpoints (Toh and Nicolson, 2009).

4.4 MTA proteins: other possible functions in cancer cells

Other reports have been forthcoming suggesting some possible roles of MTA proteins in carcinogenesis and cancer progression. The most important of these may be the relationship of MTA1 protein with c-MYC oncoprotein (Figure 2). Using expression profiling, Zhang et al. (2005) identified the MTA1 protein as a target of the c-MYC protein in primary human cancer cells. They showed that c-MYC binds to the genomic *MTA1* locus and recruits transcriptional co-activators. They also found that the MTA1 proteins in NuRD complexes were one of the first downstream targets of c-MYC function, and this was essential for the transformation potential of c-MYC. Indeed, reduction of MTA1 expression by a short hairpin RNA blocked the ability of c-MYC to transform mammalian cells (Zhang et al., 2005).
Another milestone was the establishment of a transgenic mice model that over-expressed MTA1 protein. Kumar and his collaborators found that the MTA1-transgenic mice showed inappropriate development of mammary glands. These mice also developed hyperplastic nodules and mammary tumors (Bagheri-Yarmand et al., 2004; Singh and Kumar, 2007). In this study, the underlying molecular mechanisms of MTA1 protein action and its regulation were also examined, and the results suggested that MTA1 protein dysregulation in mammary epithelium and cancer cells triggered down-regulation of the progesterone receptor-B isoform and up-regulation of the progesterone receptor-A isoform, resulting in the up-regulation of the progesterone receptor-A target genes Bcl-XL and cyclin D1 in mammary glands of virgin mice. These authors also found that spontaneous B-cell lymphomas were induced in the *MTA1*-transgenic mice (Bagheri-Yarmand et al., 2007).
Recently, Molli et al. (2008) reported that MTA1/NuRD complexes negatively regulated BRCA1 transcription by physically associating with ERE of the BRCA1 promoter in an ERα-dependent manner. This repressive effect of MTA1 on BRCA1 expression resulted in the acquisition of abnormal centrosomes and chromosomal instability (Molli et al., 2008).
The expression of MTA1 and HDAC1 proteins can also be increased by the interaction of hepatitis B virus X (HBx) protein at the transcriptional level (Yoo et al., 2008). Since MTA1 and HDAC1/2 proteins are physically associated with HIF-1α in vivo in the presence of HBx protein, HBx-induced deacetylation stabilizes HIF-1α by inhibiting proteosomal degradation. These results indicated the existence of positive cross-talk between HBx and the MTA1/HDAC complex, and it further suggests that such cross-talk may play a role in angiogenesis and metastasis of HBV-associated hepatocellular carcinomas.
Direct interactions between MTA1 protein and endophilin 3 have also been reported by Aramaki et al. (2005). This suggests that MTA1 protein might be involved in the regulation of endocytosis mediated by endophilin 3.
An important treatment modality in cancer is the use of ionizing radiation. MTA1 protein has been implicated in ionizing radiation-induced DNA damage response by regulating p53-dependent DNA repair (Li et al., 2009a).

5. *MTA*/MTA genes and proteins as new clinical targets

This review and others (Nicolson et al., 2003; Manavathi and Kumar, 2007; Toh and Nicolson, 2009) have discussed the available data on the likelyhood that MTA proteins have important and critical roles in the genesis and progression of a wide variety of cancers. MTA1 protein can be thought of as a master co-regulatory molecule (Manavathi and Kumar, 2007; Toh and Nicolson, 2009). This clearly suggests the possibility that MTA1 protein (or the *MTA1* gene or its RNA product) could be an excellent molecular target for cancer therapy as well as its use in cancer diagnosis/prognosis.
The first studies that suggested the possibility of targeting *MTA1* RNA were reported by Nawa et al. (2000) and Nicolson et al. (2003). Using antisense phosphorothioate oligonucleotides against *MTA1* mRNA, these authors found growth inhibitory effects and inhibition of invasion of human metastatic breast cancer cell lines.
Different techniques have been used to regulate *MTA1*/MTA1 expression in order to determine the effects of MTA1 protein on cellular functions. Using RNA interference (RNAi) Qian et al. (2007) inhibited MTA1 expression in a human esophageal squamous cell carcinoma cell line and demonstrated significant inhibition of in vitro invasion and migration properties of the cancer cells (Qian et al., 2005). In a metastasis model based on murine melanoma Qian et al. (2007) examined the therapeutic use of lowering MTA1

protein levels in the melanoma cells and demonstrated that down-regulation of MTA1 protein by RNAi successfully suppressed growth in vitro and experimental metastasis in vivo. Using microRNAs against *MTA1* Reddy et al. (2009) were able to inhibit the expression of MTA1 protein in human breast cancer cells, resulting in decreased cell mobility, invasiveness, anchorage-dependent growth and tumorigenicity. Results such as these suggest a potential role of the *MTA1* gene as a target for cancer gene therapy.

Other *MTA*/MTA genes and proteins may also be useful targets. For example, MTA1s may be a useful target in the treatment of breast cancer. MTA1s functions as a repressor of ERα transcriptional activity by binding and sequestering the ERα in the cytoplasm (Kumar et al., 2002). MTA1s has a unique C-terminal 33-amino acid region containing a nuclear receptor-box motif that mediates the interaction of MTA1s protein with ERα. Singh et al. (2006) showed that the MTA1s peptide containing this motif could effectively repress the ERα transactivation function, measured by estrogen-induced proliferation and anchorage-independent growth of the human breast cancer cell line MCF-7. Using an animal model they also showed the effect of MTA1s peptide in blocking tumor progression of MCF-7 breast cancer cells that over-expressed ERα (Singh et al., 2006).

The use of MTA1 protein as a target of immunotherapy has also been considered. MTA1 protein is a promising antigen for tumor rejection, because it is over-expressed in many different tumors and is only expressed at lower levels in normal tissues (Toh and Nicolson, 2009). In reviewing a model for immunotherapy Assudani et al. (2006) proposed using a vector that contained disabled infectious single cycle-herpes simplex virus (DISC-HSV). Their initial studies demonstrated the presence of immunogenic MHC class I-restricted peptides of MTA1 protein. Next, MTA1 protein was identified as a SEREX antigen, and hence it is likely to be capable of inducing a T-cell response in cancer patients (Chen and Han, 2001).

6. *MTA*/MTA genes and proteins: future directions

This and previous reviews (Toh and Nicolson, 2003; Manavathi and Kumar, 2007; Toh and Nicolson, 2009) have focused on the clinical and biological significance of the newly emerging gene family named *MTA*. The family of MTA proteins is made up of transcriptional co-repressors that function via NuRD complexes containing chromatin remodeling and histone deacetylating molecules. These actions clearly have a role in tumor formation and progression. For example, the repression of ERα trans-activation function by MTA1 protein through deacetylation of ERE chromatin of the ER-responsive genes has been the most extensively investigated, and the data clearly demonstrated that MTA1 expression results in tumor formation in mammary glands and renders breast cancer cells phenotypically more aggressive (reviewed in Manavathi and Kumar, 2007).

In addition to chromatin histones, MTA proteins also deacetylate non-histone proteins. For example, the tumor suppressor p53 protein is deacetylated and inactivated by both MTA1 and MTA2 proteins, resulting in inhibition of growth arrest and apoptosis. HIF-1α is also deacetylated and stabilized by MTA1, leading to angiogenesis. Thus, it has been proposed that MTA proteins, especially MTA1 protein, represent master co-regulatory molecules involved in the carcinogenesis and progression of various malignant tumors (Manavathi and Kumar, 2007; Toh and Nicolson, 2009). Since, it is assumed that these properties are important to the survival and progression of cancer cells, ultimately this could lead to novel clinical applications of *MTA* genes or MTA proteins as new molecular targets for cancer therapy.

There are other examples of the potential use of MTA proteins as therapeutic targets. Inhibition of MTA1 protein expression or function may enhance the chemosensitivity of cancer cells by restoring tumor suppressor function of p53, or it may inhibit tumor angiogenesis by destabilizing the angiogenesis promoting function of HIF-1α. Moreover, MTA proteins may cooperate with HDAC inhibitors, which are now expected to be the target of a new class of anticancer agents (Toh and Nicolson, 2009).

MTA1 will also be clinically useful for the prognosis or prediction of the malignant potentials of various human cancers, such as esophageal, gastric and colorectal cancers (Toh and Nicolson, 2009). Thus, evaluating the expression levels of MTA proteins in individual cases of various cancers may provide us with important clues.

Finally, the MTA proteins are clearly present in completely normal cells to provide them with certain necessary functions. Thus, it will be important to understand their physiological functions and underlying mechanisms in normal cells. For example, *C. elegans* has MTA1 homologues, egl-27 and egr-1, that function in embryonic patterning and development (Solari et al., 1999; Chen and Han, 2001), suggesting that MTA1 protein may have an embryonic developmental function. MTA1 protein is also thought to play a crucial role in postnatal testis development and spermatogenesis (Li et al., 2007a; Li et al., 2007b), and MTA1 protein is a direct stimulator of rhodopsin expression (Manavathi et al., 2007a). These are only a few of the known physiological functions of MTA1 protein (Toh and Nicolson, 2009), and it is expected that other MTA proteins have important roles in normal physiology and development. Thus, determining the normal physiological functions of MTA proteins will be absolutely necessary in understanding the pathological functions of MTA proteins in human cancers.

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This article should be referenced as such:

Toh Y, Nicolson GL. MTA1 of the MTA (metastasis-associated) gene family and its encoded proteins: molecular and regulatory functions and role in human cancer progression. Atlas Genet Cytogenet Oncol Haematol. 2011; 15(3):303-315.