Metastasis Associated Protein 1/Nucleosome Remodeling and Histone Deacetylase Complex in Cancer

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Abstract

Cancer cells frequently exhibit deregulation of coregulatory molecules to drive the process of growth and metastasis. One such group of ubiquitously expressed coregulators is the metastasis-associated protein (MTA) family, a critical component of nucleosome remodeling and histone deacetylase (NuRD) complex. MTA1 occupies a special place in cancer biology due to its dual corepressor or coactivator nature and widespread overexpression in human cancers. Here, we highlight recent advances in our understanding of the vital roles of MTA1 on transformation, epithelial-mesenchymal transition, and on the functions of key cancer-relevant molecules as a nexus of multiple oncogenes and tumor suppressors. In addition to its paramount role in oncogenesis, we also reveal several new physiological functions of MTA1, related to DNA-damage, inflammatory responses and infection, in which MTA1 functions as a permissive "gatekeeper" for cancer-causing parasites. Further, these discoveries unraveled the versatile multidimensional modes of action of MTA1, which are independent of the NuRD complex and/or transcription. Given the emerging roles of MTA1 in DNA repair, inflammation, and parasitism, we discuss the possibility of MTA1 targeted therapy for use in not only combating cancer but also other inflammation and pathogen-driven pathological conditions.

Keywords

Master Coregulator; Cancer; DNA-damage Response; Inflammation; Pathogen-driven Cancers

Introduction

Cancer is a collection of cumulative phenotypic changes that are caused by dysregulated genetic and epigenetic processes including, aberrant transcription of genes that drive cell survival, proliferation, immunological functions, invasion, and metastasis (1). Gene transcription is a highly ordered but dynamic process that is tightly regulated by sequence-specific transcription factors (TFs) and associated coregulatory proteins (2). Coregulators control TF-dependent gene expression through direct binding to TFs as well as indirectly by interacting with histones and thereby regulating the accessibility of TFs to DNA, resulting in the stimulation or repression of the transcription of specific genes (3). Accordingly,

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coregulators that activate gene transcription are referred to as co-activators while those that repress it are known as co-repressors, and those with both functions, in a context-dependent manner, are dual coregulators.

The critical role of coregulators in cancer is evident from the fact that cancer cells often overexpress "growth coactivators" and hijack these molecules to drive proliferation and other processes that are characteristics of a cancer cell. One group of ubiquitously expressed coregulators is the metastasis-associated protein (MTA) family, comprising six different gene products (MTA1, MTA1s, MTA1-ZG29p, MTA2, MTA3, and MTA3L) that originate from three different genes (4–8). MTA1, the founding member of the MTA family (9), holds a special place among the family and among coregulators due to several reasons such as its ability to repress or stimulate transcription in a context-dependent manner, controlling the steady-state of proteins via affecting protein ubiquitination, contributing to the DNA damage response, and maintaining an overexpressed state in a wide variety of human epithelial and hematological malignancies (5–7). Here, we highlight recent advances in our understanding of the key roles of MTA1 in the NuRD-complex that happen in a transcription-dependent or -independent manner, in processes that govern oncogenesis, epithelial-mesenchymal transition, DNA damage response, inflammation, and pathogen-driven cancers (Fig. 1).

Tracing the MTA1 Path to Cancer Progression

Despite the paramount importance of MTA1, its molecular functions remained a mystery until 1998 (Fig. 1A) when a proteomic analysis identified MTA1 as an integral component of the nucleosome remodeling and histone deacetylase (NuRD) complex (10), providing clues about possible functions of MTA1 in chromatin remodeling. However, its direct role in chromatin remodeling remained unknown until 2001 (Fig. 1A) when estrogen receptor-α (ERα) became the first direct target of MTA1 (11), establishing a direct link between MTA1 and the NuRD complex in the transcriptional repression of a specific gene. In addition, these findings also provided the first chromatin remodeling-based mechanism by which MTA1 overexpression may contribute to tamoxifen-resistant and aggressive phenotypes of human breast cancer by blocking the transactivation activity of ERα. Those early discoveries opened the door for a new era in elucidating the mechanistic role of MTA1 in cancer progression as well as its physiological functions. However, growing bodies of evidence have now firmly established that MTA1 functions are not limited to the MTA1/NuRD complex and/or its transcriptional effects as originally presumed.

Several studies over the past two decades have identified MTA1 as one of the most commonly overexpressed gene products in human cancers (Table S1). The mechanism involved has been proposed to be either transcriptional regulation or post-translational modifications, or both (see below). In addition, MTA1 is also detected in most normal mouse tissues, with significant levels present in brain, lung, ovary, mammary gland, and testis (11, 12). In general, MTA1 levels are upregulated in metastatic and/or aggressive cancer cell lines and tumors as compared to its levels in low metastatic cell lines and/or tumors (7–9), and are correlated with tumor progression and poor prognosis (Table S1). These observations are consistent with the original cloning of MTA1 as a differentially expressed gene from a rat metastatic mammary gland cell line (9). However, the hypothesis of a mechanistic role of MTA1 in cancer progression remained unsupported until 2001 when overexpression of MTA1 alone was able to confer an anchorage-independent phenotype to a non-invasive breast cancer cell line (11) while selective depletion of MTA1 by siRNA reduced the invasiveness (13).

The second set of observations that tied MTA1 overexpression a step closer to cancer, include the development of the first transgenic murine model expressing human MTA1

under the control of the mouse mammary tumor virus promoter (Fig. 1A) (14). It was observed that MTA1 overexpression could lead to the development of ductal hyperbranching and hyperplasic nodules in virgin glands, presumably due to the activation of anti-apoptotic B-cell lymphoma-extra large (Bcl-xl) and oncogenic cyclin D1 pathways, as well as the formation of mammary gland adeno-carcinomas in the older animals (14). This provided support to the notion of a potentially causative role of MTA1 in mimicking critical stages of tumor development in a physiologically relevant whole-animal model. Consistent with a hormone-independent mechanistic role of MTA1 (11), MTA1 overexpression also triggered hyperplasia in the mammary gland in both ovartazid female as well as male mice (14). Interestingly, most of the MTA1-MMTV-transgenic mice also developed widespread metastases to various organ systems over time (15). This provided the first experimental animal model that showed spontaneous metastasis driven by the MTA1-transgene. Surprisingly, most of these metastases were of lymphatic origin with diffuse large B-cell lymphomas (DLBCL), and accompanied by an upregulation of Pax5, a B-cell specific transcriptional factor (16) *via* MTA1/Pol II but not the NuRD complex, as was the case with the transcription of the BCAS3 coactivator (17). These findings were also relevant to human DLBCL because of a wide-spread co-overexpression of MTA1 and Pax5 in such specimens (16).

A definitive role of MTA1 in oncogenesis is also supported by the ability of MTA1 overexpression to transform the Rat1 fibroblasts by direct repression of Gi2alpha transcription owing to the corepressor activity of the MTA1/NuRD complex (Fig. 1B, left panel)(18). Since Gi2alpha negatively regulates the trimeric G-protein cycle, MTA1 repression of Gi2alpha resulted in a profound hyperstimulation of the Ras-Raf pathway(18). In fact, this study also found evidence of a close correlation between the levels of MTA1 and ERK1/2 activation, a downstream component of the Ras pathway, in a large cohort of breast tumors. Given the critical role of ERK in the Wnt/β-catenin pathway, which is aberrantly activated in human breast cancer (19), and the synergistically elevated levels of MTA1 and ERK activation, the hypothesis that MTA1 upregulation may contribute to canonical Wnt-signaling was formed. Furthermore, virgin mammary glands from MTA1 transgenic mice also show upregulation of two Wnt1 targets, β-catenin and cyclin D1. However, in spite of widely reported, increased Wnt1 expression in cancer, upstream modifiers that regulate the transcription of the Wnt1 gene in mammary epithelial cells are still not well-defined. In this context, two recent studies have revealed a definitive role of MTA1 in the stimulation of canonical Wnt1-signaling (Fig. 1B, middle panel)(20, 21). It was found that MTA1 stimulates the transcription of *Wnt1* itself, and consequently, Wnt1 signaling, via repressing the *Six3* homeodomain gene, which functions as a potent corepressor of *Wnt1* transcription (20, 21). Consistent with a critical role of MTA1 in cancer progression, MTA1 is also essential for transformation by another well-studied oncogene, c-Myc- a target of a large number of signaling cascades (22). Experimental depletion of MTA1 severely compromises the ability of c-Myc to manifest its transforming activity (22). In brief, MTA1 represents and regulates nexuses of multiple oncogenes and qualifies to be labeled as a "regulator-of-regulators" of transformation (Fig. 1B).

Interaction of MTA1 with Tumor Suppressors

The process of oncogenesis is profoundly influenced by the status, activity, and upstream regulators of tumor suppressors which play a fundamental role in counteracting dysregulated cell proliferation. Since detectable levels of MTA1 are found in most normal cells, cancer progression and interaction with tumor suppressors, in general, occurs when the "fine-balance" and equilibrium of the level of MTA1 (i.e. overexpression beyond a threshold) is disrupted (Fig. 1C). Therefore, to understand the impact of MTA1 in cancer biology, it is essential to reveal its role in normal cells. In this context, emerging data suggest repression

of the transcription of a tumor suppressor gene, *breast and ovarian cancer susceptibility protein 1 (BRCA1)* by MTA1 *via* physical recruitment of the MTA1/NuRD complex to an estrogen-responsive element in the *BRCA1* promoter (23). It is noteworthy that the down-regulation or dysfunction of BRCA1 leads to accelerated tumor growth and metastasis (24) and therefore it remains possible that MTA1 inhibition of BRCA1 might contribute to the malignant transformation of normal cells.

The MTA1/NuRD complex was also identified as a transcriptional co-repressor of tumor suppressors, $p21^{WAF1}$ (25) and hypermethylated in cancer 1 (HIC1)(26), both of which are direct targets of p53 (27, 28). The $p21^{WAF1}$ protein promotes cell cycle arrest in response to many stimuli and functions as both a sensor and an effector of multiple anti-proliferative signals (29). HIC1 also play a role in the early stages of tumor progression, and HIC1 is shown to be hypermethylated and transcriptionally silent in several types of human cancer (30). MTA1 is reported to associate (31, 32) and deacetylate p53 (32, 33), and therefore it is also possible that MTA1 might indirectly modulate the levels of p53-regulated genes such as $p21^{WAF1}$ and *HIC1* by affecting the transcriptional activity of p53. However, several lines of experimental, genetic investigations from MTA1-knockout mice showed that p53 stabilization by MTA1 through competition with E3 ubiquitin ligase constitutive photomorphogenesis protein 1 (COP1) in p53 binding as well as destabilization of COP1 and murine double minute 2 (31) occurs in an MTA1/NuRD complex independent manner. In addition, the MTA1/NuRD complex is also known to directly repress the transcription of $p21^{WAF1}$ in a p53-independent manner in the p53-null murine embryonic fibroblasts (MEFs) (25). Furthermore, a recent microarray-based analysis of p53-knockout MEFs overexpressing MTA1 uncovered a whole range of p53-independent MTA1 regulated genes(34), highlighting the significance of MTA1 in cancer biology in both a p53-independent and -dependent manner.

Apart from the aforementioned tumor suppressors, MTA1 is shown to regulate another p53-associated tumor suppressor gene, alternative reading frame (ARF) (also known as p14ARF in humans and p19ARF in mice), which plays an important protective role in oncogenic transformation and tumorigenicity (35). A recent study discovered MTA1 as a novel transcriptional coactivator of the *ARF* gene. This happens through the recruitment of the transcription factor c-Jun onto the *ARF* promoter in a p53-independent manner. Interestingly, ARF, in turn, negatively regulates MTA1 expression independent of p53 and c-Myc *via* both transcriptional and post-translational mechanisms (36). Thus, MTA1-mediated activation of ARF and ARF-mediated inhibition of MTA1 represent a p53-independent, bidirectional, autoregulatory mechanism in which these two opposites act in concert to regulate cell homeostasis and oncogenesis, depending on the cellular context and the environment (36). Given the putative growth suppressive roles of p53 and ARF, and the oncogenic activity of MTA1, it seems a paradox that MTA1 positively regulates both tumor suppressors (Fig. 1C). However, these findings indicate the "fail-safe" mechanism that is maintained in normal mammalian cells which safeguards the cells against oncogenic stimuli. Given the fact that the tumor suppressor p53 is mutated or deleted in more than 50% of human cancers (37), and the INK4a/ARF locus is found to be deleted or silenced in about 30% of all known types of malignancies (38), these genetic perturbations could help cancer cells override the normal mechanisms controlling cellular proliferation. Thus, it is a real possibility that the loss or silencing of p53 or ARF could contribute to MTA1-driven oncogenesis and tumor progression.

As discussed above, MTA1 has important functions in regulating gene transcription, but this might not be the only mechanism by which it contributes to oncogenesis. In this respect, MTA1 is shown to interact with several cancer-related proteins and these associations have also been implicated in oncogenesis. One such example is the tumor suppressor protein

COP1, which functions as an E3 ubiquitin-protein ligase and targets protein substrates for ubiquitination and degradation. COP1 also acts as a tumor suppressor by negatively regulating the stability of the proto-oncogenes ETV1 (39) and c-Jun (40). A recent study found that MTA1 promotes auto-ubiquitination and degradation of COP1, revealing an additional level of MTA1 participation in oncogenesis by blocking the tumor suppressor activity of COP1 (41). Interestingly, COP1, in turn, targets MTA1 for ubiquitination and destruction by acting as an ubiquitin protein ligase (41). This finding partially explains why MTA1 is dominantly overexpressed in human cancer. Thus, both MTA1 and COP1 proteins form double vicious cycles, contributing to uncontrolled growth regulation. Similarly, the interaction between MTA1 and BRCA1 tumor suppressor which possesses an intrinsic E3 ubiquitin-protein ligase activity could also have parallel bidirectional auto regulation that might enable oncogenesis.

Dysregulated MTA1 Promotes Epithelial-Mesenchymal Transition

Since the overexpression but not normal levels of MTA1, is responsible for oncogenesis, an immediate compelling question about the upstream signals or factors that trigger MTA1 upregulation in human cancer is raised. A recent study identified transforming growth factor-β1 (TGF-β1) as a potent inducer of *MTA1* transcription and expression as well as MTA1 as a downstream effector of TGF-β1 which mediates repression of epithelial-cadherin (E-cadherin) expression (Fig. 1B, right panel) (42). E-cadherin plays an important role in epithelial cell-cell adhesion and in the maintenance of tissue architecture. Therefore reduction or loss of E-cadherin expression promotes epithelial-to-mesenchymal transition (EMT) and tumor progression (43). The underlying basis of MTA1 mediated regulation of E-cadherin includes the dual coregulatory nature of MTA1 wherein the MTA1/Pol II coactivator complex stimulates the expression of FosB which, in-turn, interacts with MTA1/NuRD corepressor to inhibit the transcription of E-cadherin(42). Thus, activation of the TGF-β1-MTA1-E-cadherin axis is emerging as a central feature of EMT and metastasis in epithelial cells. In addition, MTA1 has also been shown to activate two related transcription factors SNAI1 and SLUG (also known as SNAI2) in ovarian cancer cells (44), although the details of this mechanism remain to be determined. Both SNAI1 and SLUG (45) proteins are direct transcriptional repressors of E-cadherin and their expression induces EMT. Thus, it is possible that oncogenic MTA1 exploits multiple signaling pathways to activate EMT programs, directly or indirectly, during cancer invasion and metastasis. In agreement with this notion, several recent findings show MTA1 to interject into the hypoxia-inducible factor 1α (46, 47) and Wnt1 pathways (20), which have been implicated in EMTs through multiple distinct mechanisms (48).

MTA1, a New Target and Component in the DNA Damage Response

Due to the paramount role of MTA1 in human cancer, it is reasonable to expect MTA1 to play a crucial role in the DNA repair process. In fact, a set of recent studies have discovered an essential role of MTA1 in the DNA damage response and more importantly, a cancer-relevant physiologic function of the normal levels of MTA1 in eukaryotic cells (Fig. 1D)(25, 31, 41, 49–51). Surprisingly, the involvement of MTA1 in DNA damage can be traced back to 1999, when Schmidt et al. found that DNA damage checkpoint protein ATR (ataxia telangiectasia mutated-and Rad3-related) associates with multiple components of the NuRD complex, which includes MTA1 (52). Ten years later in 2009, substantial molecular and genetic experimental evidence established a previously unrecognized functional role of MTA1 in ionizing radiation (IR)-induced double-strand break (DSB) repair (41). The genetic depletion of MTA1 renders cells to be hypersensitive to IR exposure, suggesting a defect in DSB repair in MTA1-deficient cells. Reassuringly, re-expressing MTA1 in such cells could rectify these defects, indicating the involvement of MTA1 in efficient DSB

repair (41). The underlying mechanism by which MTA1 facilitates DNA repair is shown to occur in a p53-dependent and -independent manner (25, 31). Interestingly, this function of MTA1 might be conserved in MTA2 (53). However, this was not manifested in MTA1-knockout cells where the remaining members of the MTA family were unable to rescue the noted defects in DNA repair, highlighting the power of genetic supporting evidence. Further, the DNA damage role of MTA1 was emphasized by evidence that demonstrates the recruitment of MTA1 to sites of DNA damage in a poly(ADP-ribose) polymerase (PARP)-dependent manner, and depletion of MTA1 by siRNAs resulted in an increased cell sensitivity to IR in human cancer cells (50). These finding were strongly substantiated by several recent reports that highlight the role of CHD4 (50, 53–55) and HDAC1/2 (56, 57) in DNA damage repair. Together, it is becoming increasingly clear that multiple components of the NuRD complexes are indeed, implicated in DNA damage repair, emphasizing the evolutionarily conserved functions of this family of chromatin-remodeling complexes in DNA repair.

In addition to DSB, MTA1 is equally essential for ATR-mediated DNA damage checkpoint function following ultraviolet (UV) radiation (49). In this context, MTA1 is required for the activation of the ATR-Claspin-checkpoint kinase 1 (Chk1) and ATR-H2AX pathways following UV treatment, and consequently, depletion of MTA1 results in the G2-M checkpoint defect and increases cellular sensitivity to UV-induced DNA damage (49). Together, these findings established the significant function of MTA1 in facilitating the repair of the damaged DNA, and hence survival of cancer cells, in the face of the severe, endogenous, oncogene-induced DNA damage as well as the damage induced by genotoxic therapy(58). Such a concept is plausible because the status of MTA1 might not only promote the fitness of cancer but also regulate the sensitivity of tumor cells to genotoxic therapy, as experimental depletion of MTA1 can enhance radio-sensitivity of the cultured cells to radiation. Based on these findings, MTA1-targeting approaches are likely to increase therapeutic benefits of radiation therapy in cancer.

MTA1, A Bridge between Inflammation and Cancer

Accumulating clinical, epidemiological, and molecular evidence has led to a generally accepted notion that inflammation and cancer are intimately linked and persistent inflammation over time, contributes towards the molecular processes involved in cancerous phenotypes (59, 60). Most of these pathways converge onto a central transcriptional player, nuclear factor-κB (NF-κB) (61), which in-turn, orchestrates a complex set of reactions involving multiple negative- and positive-feedback loops by virtue of transcriptional regulation. While searching for the upstream activator of MTA1, Pakala et al. recognized the presence of multiple NF-κB consensus motifs in the *MTA1* promoter and for the first time showed MTA1 as an NF-κB-target gene and a primary target of inflammation (62). Accordingly, stimulation of macrophages with lipopolysaccharide (LPS), a prototypical endotoxin in response to various infections, stimulates *MTA1* transcription *via* the NF-κB pathway as well as expression of NF-κB-target cytokines(62). Interestingly, MTA1 in-turn, became instrumental for the production of NF-κB-mediated pro-inflammatory cytokines, such as interleukin-1β, tumor necrosis factor α (TNFα), and macrophage inflammatory protein-2 in LPS-stimulated macrophages (Fig. 1E)(62). These findings also discovered MTA1's corepressor or coactivator differential regulation of NF-κB-target genes under basal or stimulated conditions via MTA1/HDAC or MTA1/Pol II complexes, and thus function as one of the core referees that coordinate the details of the NF-κB signaling network and homeostasis maintenance during inflammatory responses(62). Since many of the protein components of NF-κB signaling are NF-κB-targets, subsequent studies found MTA1 protein to be involved in the regulation of the expression of myeloid-differentiation factor 88 (63) and transglutaminase 2(64), both key components of NF-κB signaling in a variety of

inflammatory diseases and human cancers. These recent reports established MTA1 as a target and an essential component of the inflammatory response (Fig. 1E).

MTA1, A Host Master Router in Infectious Agent-driven Cancer

In keeping with its role as a primary target of inflammation (62–64), MTA1 is shown to be involved in the optimum stimulation of Hepatitis B virus (HBV) x-protein (HBx)-triggered NF-κB signaling as well as the expression of NF-κB targets genes, such as TNF-α, cyclooxygenase-2 (COX2), and inducible nitric oxide (Fig. 1E) (65, 66). Interestingly, MTA1, an established NF-κB-target gene, was also found to be upregulated by HBx, which fuels the amplification and duration of NF-κB signaling. Furthermore, both MTA1 and NF-κB are co-overexpressed in human liver cancer, which is positive for the HBx protein (65). Together, these observations suggest MTA1 status to be an important element that contributes to inflammation prolongation, and in-turn, HBV-driven liver tumorigenesis.

Schistosoma haematobium is classified as a group 1 carcinogen by the WHO and is established to cause bladder cancer and fibrosis in the liver, as a result of chronic inflammation. MTA1 is reported to be essential for the optimal growth of schistosomes to adulthood and successful parasitism in a murine MTA1-knockout experimental model (Fig. 1E) (67). The underlying mechanism included deregulation of cytokine interdependence and regulated Th1/Th2 cytokine responses, presumably largely due to chromatin remodeling of its immune targets in the MTA1-knocout mice. Similarly, the carcinogenic liver fluke *Opisthorchis viverrini,* which is responsible for inflammation-associated development of human cholangiocarcinomas also requires the MTA1 coregulator for survival in a murine model (Fig. 1E)(68). Relevance of these studies to humans was proved by IHC studies of ~300 liver tissue cores from confirmed cases of *Opisthorchis viverrini,* showing a widespread upregulation of MTA1 expression in the specimens(68). These findings suggest MTA1 to function as a host permissive factor for the optimal mediation of the infectious process of human helminth parasites which cause cancer. Collectively, these recent findings, for the first time, have revealed an inherent role of MTA1 in parasitism and cancer and thus, have opened new avenues of exciting research that would be beneficial for cancer patients globally, both in affluent and resource-limited settings.

The Next Horizon for MTA1 Research

Since the isolation of the MTA1 cDNA in 1994 (9), remarkable progress has been made in our understanding of the functions of MTA1, not only in human cancer but also in several other physiological processes such as the DNA-damage response, inflammation and immune modulation (Fig.1A). However, there are still many questions that remain to be answered. For instance, the triggers which disrupt the MTA1 equilibrium and allow it to manifest oncogenic activity as well as the normal cellular functions of MTA1 still remain to be defined. This equilibrium could be fine-tuned by post translational modifications of MTA1 but a comprehensive understanding about the cross-talks between these modifications needs to be characterized. We began to appreciate the physiological functions of MTA1 in various pathways and these emerging studies already suggest other significant physiological roles of MTA1. Therefore, redefining the nomenclature of MTA1 away from metastasis and reflecting on its complete characteristics should be considered. The snapshots of MTA1 functions show its co-repressor and co-activator abilities but how MTA1 deals with this conundrum and the determining elements of MTA1 that decide that this molecular switch will act as an activator or repressor is one of the central mechanistic questions to be resolved. This might be understood through studies that modulate MTA1 in a signal-dependent post-translational way, generating the code which might dictate its engagement in co-repressor vs. co-activator complexes. To understand the complete molecular mechanism

of MTA1, high resolution crystal structures of MTA1 are needed. The authors hope to bring such on-going efforts to a meaningful conclusion in the near future. Such information will also pave the way for the rationale development of the target-specific cancer therapeutics. Given the emerging role of MTA1 in DNA repair, targeting MTA1 might prove efficacious when used in combination with DNA-damaging chemotherapeutic drugs and radiotherapy. More significantly, the host permissive nature of MTA1 allows it to be an effective drug target for pathogen-driven cancers which are prevalent in countries with limited economic resources. In summary, the past decade of research on MTA1 drastically transforms our understanding of the abilities and influences of coregulators and therefore we hope to realize the possibility of MTA1 targeted therapy against not only cancer but also several inflammation and pathogen-driven pathological conditions such as arthritis, atherosclerosis and respiratory disorders.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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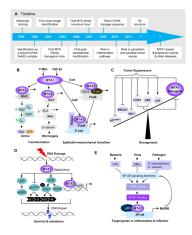
Figure 1.
Diverse functions of the MTA1/NuRD complex in cancer. (A) Timeline of major advance in the MTA1 research. (B) Role of MTA1 in the cell transformation and epithelial-mesenchymal transition through multiple signaling pathways. (C) Interaction of MTA1 with tumor suppressors. (D) Emerging role of MTA1 in DNA damage response through p53-depdnent and – independent mechanism. (E) MTA1 is a key molecular link between inflammation and cancer, and plays a critical role in infectious agent-driven cancer. CoA, co-activator; CoR, co-repressor.