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 the nucleosome remodeling and histone deacetylase (NuRD) complex. MTA1 occupies a special place in cancer biology because of 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 the functions of key cancer-relevant molecules such as a nexus of multiple oncogenes and tumor suppressors. In addition to its paramount role in oncogenesis, we reveal several new physiologic functions of MTA1 related to DNA damage, inflammatory responses, and infection, in which MTA1 functions as a permissive “gate keeper” 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 not only in combating cancer but also in other inflammation and pathogen-driven pathologic conditions. Cancer Res; 72(2); 387–94. © 2012 AACR.

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, immunologic functions, invasion, and metastasis (1). Gene transcription is a highly ordered but dynamic process that is tightly regulated by sequence-specific transcription factors and associated coregulatory proteins (2). Coregulators control transcription factor–dependent gene expression through direct binding to transcription factors, as well as indirectly by interacting with histones and thereby regulating the accessibility of transcription factor to DNA, resulting in the stimulation or repression of the transcription of specific genes (3). Accordingly, coregulators that activate gene transcription are referred to as coactivators, whereas those that repress it are known as corepressors, 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 6 different gene products (MTA1, MTA1s, MTA1-ZG29p, MTA2, MTA3, and MTA3L) that originate from 3 different genes (4–8). MTA1, the founding member of the MTA family (9), holds a special place among MTA family members and coregulators for several reasons, such as repressing or stimulating 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 hematologic malignancies (5–7). Here, we highlight recent advances in our understanding of the key roles of MTA1 in the nucleosome remodeling and histone deacetylase (NuRD) complex, which happen in a transcription-dependent or transcription-independent manner, in processes that govern oncogenesis, epithelial–mesenchymal transition (EMT), 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 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 was identified as the first direct target of MTA1 (11), establishing a direct link between MTA1 and the NuRD complex in the transcriptional repression. 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 estrogen receptor-α. Those early discoveries opened the door for a new era in elucidating the mechanistic role of MTA1 in cancer progression, as well as its physiologic 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 2 decades have identified MTA1 as one of the most commonly overexpressed gene products in human cancers (Supplementary Table S1). The mechanism involved has been proposed to be either transcriptional regulation, posttranslational modifications, or both (see below). 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 with their levels in low metastatic cell lines and/or tumors (7–9), and are correlated with tumor progression and poor prognosis (Supplementary 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 noninvasive breast cancer cell line (11), whereas selective depletion of MTA1 by siRNA reduced the invasiveness (13).

The second set of observations that tied MTA1 overexpression 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; ref. 14). It was observed that MTA1 overexpression could lead to the development of ductal hyperbranching and hyperplastic nodules in virgin glands, presumably because of the activation of antiapoptotic B–cell lymphoma–extra large (Bcl-x) and oncogenic cyclin D1 pathways, as well as the formation of mammary gland adenocarcinomas in the older animals (14). This finding 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 overiectomized female and male mice (14). Interestingly, most of the MTA1-MMTV–transgenic mice also developed widespread metastases to various organ systems over time (15). This study 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 and accompanied by an upregulation of Pax5, a B–cell–specific transcriptional factor (16) via MTA1/PoI 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 diffuse large B–cell lymphoma because of a wide-spread co-overexpression of MTA1 and Pax5 in such patients (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; refs. 18). Because 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 extracellular signal–regulated kinase 1/2 (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 show upregulation of 2 Wnt1 targets, β-catenin and cyclin D1. However, despite 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, 2 recent studies have revealed a definitive role of MTA1 in the stimulation of canonical Wnt1 signaling (Fig. 1B, middle panel; refs. 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 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 that play a fundamental role in counteracting dysregulated cell proliferation. Because detectable levels of MTA1 are found in...
most normal cells, cancer progression and interaction with tumor suppressors, in general, occur 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 downregulation 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 corepressor of tumor suppressors p21\(^{WAF1}\) (25) and hypermethylated in cancer 1 (HIC1; ref. 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 effecter of multiple antiproliferative signals (29). HIC1 also plays 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 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 known to directly repress the transcription of p21\(^{WAF1}\) in a p53-independent manner in the p53-null murine embryonic fibroblasts (25). Furthermore, a recent microarray-based analysis of p53-knockout murine embryonic fibroblasts 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 p53-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 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 posttranslational mechanisms (36). Thus, MTA1-mediated activation of ARF and ARF-mediated inhibition of MTA1 represent a p53-independent, bidirectional, autoregulatory mechanism in which these 2 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 that 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 autoregulation that might enable oncogenesis.

Dysregulated MTA1 Promotes Epithelial–Mesenchymal Transition

Given the fact that overexpression of MTA1 is implicated in oncogenesis, an immediate compelling question about the upstream signals or factors that trigger MTA1 upregulation in human cancer is raised. A recent study identified 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; ref. 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 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 been shown to activate 2 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 interact 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

Owing 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; refs. 25, 31, 41, 49–51). Surprisingly, the involvement of MTA1 in DNA damage can be traced back to 1999, when Schmidt and colleagues found that the DNA damage checkpoint protein ataxia telangiectasia mutated- and Rad3-related (ATR) 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–induced double-strand break (DSB) repair (41). The genetic depletion of MTA1 renders cells hypersensitive to ionizing radiation exposure, suggesting a defect in DSB repair in MTA1-deficient cells. Reassuringly, reexpressing 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 p53-independent manner (25, 31). Interestingly, this function of MTA1 might be conserved in MTA2 (53). However, this was not manifested in MTA1-knockout cells in which the remaining members of the MTA family were unable to rescue the noted defects in DNA repair, highlighting the nonredundant role of MTA1 in DNA damage response. Further, the DNA damage role of MTA1 was emphasized by evidence that shows the recruitment of MTA1 to sites of DNA damage in a PARP-dependent manner, and depletion of MTA1 by siRNAs resulted in an increased cell sensitivity to ionizing radiation in human cancer cells (50). These findings were strongly substantiated by several recent reports that highlight the role of CHD4 (50, 53–55) and histone deacetylases 1 and 2 (HDAC1/2; refs. 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 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 to 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, epidemiologic, and molecular evidence has led to a generally accepted notion that inflammation and cancer are intimately linked and that persistent inflammation over time contributes toward the molecular processes involved in cancerous phenotypes (59, 60). Most of these pathways converge onto a central transcriptional player, 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 and colleagues 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, 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 proinflammatory cytokines, such as interleukin-1β, TNF-α, and macrophage inflammatory protein-2 in lipopolysaccharide-stimulated macrophages (Fig. 1E; ref. 62). These findings also discovered MTA1’s co repressor 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). Because 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-kB signaling as well as the expression of NF-kB target genes, such as TNF-α, COX2, and inducible nitric oxide (Fig. 1E; refs. 65, 66). Interestingly, MTA1, an established NF-kB target gene, was also found to be upregulated by HBx, which fuels the amplification and duration of NF-kB signaling. Furthermore, both MTA1 and NF-kB 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 hematobium_ is classified as a group 1 carcinogen by the World Health Organization 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; ref. 67). The underlying mechanism included deregulation of cytokine interdependence and regulated Th1/Th2 cytokine responses, presumably largely because of chromatin remodeling of its immune targets in the MTA1-knockout mice. Similarly, the carcinogenic liver fluke _Opisthorchis viverrini_, which is responsible for inflammation-associated development of human cholangiocarcinomas, requires the MTA1 coregulator for survival in a murine model (Fig. 1E; ref. 68). Relevance of these studies to humans was proved by immunohistochemical studies of ~300 liver tissue cores from confirmed cases of _O. 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 that 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 physiologic processes such as the DNA damage response, inflammation, and immune modulation (Fig. 1A). However, many questions still remain to be answered. For instance, the triggers that disrupt the MTA1 equilibrium and allow it to manifest oncogenic activity, as well as the normal cellular functions of MTA1, remain to be defined. This equilibrium could be fine tuned by posttranslational modifications of MTA1, but a comprehensive understanding about the cross-talk between these modifications needs to be characterized. We began to appreciate the physiologic functions of MTA1 in various pathways, and these emerging studies already suggest other significant physiologic 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 corepressor and coactivator abilities, but how MTA1 deals with this conundrum and the determining elements of MTA1 that allows this molecular switch to act as an activator or repressor is one of the central mechanistic questions to be resolved. This question might be understood through studies that modulate MTA1 in a signal-dependent posttranslational way, generating the code that might dictate its engagement in corepressor versus coactivator complexes. To understand the complete molecular mechanism of MTA1, high-resolution crystal structures of MTA1 are needed. The authors hope to bring such ongoing efforts to a meaningful conclusion in the near future. Such information will also pave the way for the rational development of 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 that 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 pathologic conditions, such as arthritis, atherosclerosis, and respiratory disorders.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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