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Review

Metastasis-associated protein 1: a druggable target in cancer treatment

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Cancer treatment has undergone significant transformation with the emergence of molecularly targeted drugs, aiming to exploit specific vulnerabilities within cancer cells while sparing normal tissues. One critical aspect of this approach is the identification of druggable targets, proteins or pathways that can be modulated by pharmacological agents to inhibit tumor growth or metastasis. The metastasis-associated protein 1 (MTA1) has emerged as a promising druggable target due to its multifaceted roles in cancer progression, including regulation of gene expression, chromatin remodeling, and promotion of epithelial-mesenchymal transition. This abstract provides an overview of the current landscape of MTA1 as a druggable target in cancer therapy, highlighting its diverse functions across different malignancies and its potential as a predictive biomarker for therapeutic response. Finally, it explores future directions and novel strategies for exploiting MTA1 inhibition in precision oncology. Overall, understanding the druggable potential of MTA1 offers new avenues for the development of innovative cancer treatments with improved efficacy and reduced toxicity, ultimately leading to better clinical outcomes for cancer patients.

Keywords: Nurd complex, Lung neoplasms, Colorectal neoplasms, Prostate neoplasms, MTA1

INTRODUCTION

Metastasis-associated genes (MTAs) play a critical role in cancer invasion and metastasis. MTAs make up a rapidly expanding gene family with three known genes: MTA1, MTA2, and MTA3. In particular, MTA1 acts as a transcriptional regulator that induces epithelial-mesenchymal transition (EMT) in various solid tumors. It is the first gene discovered in mice, was identified in 1994 [1]. In humans, the MTA1 gene consists of 21 sections and can produce 20 different transcripts through alternative splicing. These transcripts encode proteins that play crucial roles in regulating gene expression and are particularly significant in the development and spread of various cancers, including breast, liver, colon, pancreas, prostate, blood, esophageal, and gastrointestinal cancers. The MTA1 protein, with 715 amino acids, is longer than MTA2 and MTA3, which contain 668 and 594 amino acids, respectively [1]. MTA proteins are integral components of the NuRD complex (nuclear remodeling and deacetylation complex) and are believed to modulate transcription by influencing chromatin remodeling [2]. MTA1, in particular, is strongly associated with the aggressiveness of several cancers and is considered a potential target for cancer therapy [3]. Additionally, MTA1 exhibits various functions independent of the NuRD complex, contributing to cancer progression and metastasis through its interaction with genes and proteins involved in processes such as transformation, growth, invasion, survival, and resistance to therapy. Ongoing research on MTA1 aims to better understand its crucial roles in cancer development, metabolism, and inflammation. MTAs are a type of gene that is involved in the spread of cancer. MTA1 is especially important in many types of cancers, and scientists are studying it to find new ways to treat cancer. It is also involved in other processes in the body, and understanding how it works could help us find new treatments for different diseases.

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STRUCTURAL AND FUNCTIONAL ROLE OF MTA1 IN NuRD COMPLEX

In humans, a collection of proteins known as the NuRD complex plays a crucial role in the regulation of our genetic material. This

complex is involved in compacting the genetic material by removing certain chemical groups from nucleosomes, which are the basic structural units of the genetic material. The NuRD complex is vital for maintaining the stability, development, and repair of the genes present in our body. At its core, the NuRD complex consists of three key proteins: HDAC1, which is responsible for removing certain chemical groups from nucleosomes; MTA1, which acts as a scaffold to hold the complex together; and RBBP4, which facilitates the interaction of the complex with nucleosomes. MTA1, one of the proteins in the NuRD complex, is found to be upregulated in various cancer tissues [4]. The structure of MTA1 includes several distinct domains, indicating specific functions within the protein. The amino-terminal region contains four established domains: an amino-terminal BAH domain, followed by ELM2 and SANT domains and a GATA-like zinc finger domain towards the center of the protein [5]. Bioinformatics analysis of MTA1 suggests the presence of specific structural characteristics, such as predicted disorder regions between certain domains. This insight implies that the MTA1:HDAC1:RBBP4 proteins may form a structural core of the NuRD complex with a fixed arrangement of subunits [6]. Furthermore, the NuRD complex is composed of two functionally distinct sub complexes: a chromatin remodeling sub complex and a deacetylase sub complex. The chromatin remodeling sub complex includes proteins involved in altering the structure of the genetic material, while the deacetylase sub complex contains proteins responsible for removing certain chemical tags from the genetic material [7]. Among the subunits of the NuRD complex, the MTA family members have been extensively studied in the context of cancer development (Fig. 1).

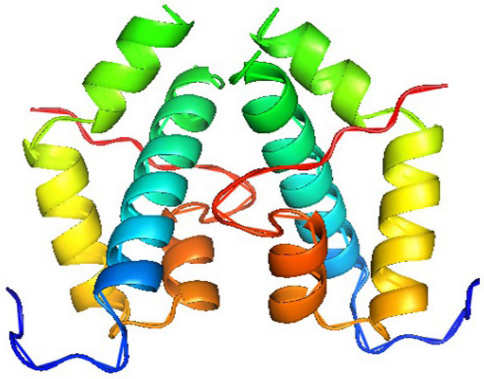

Fig. 1. Metastasis-associated protein 1 (MTA1) dimer in NuRD complex.

MTA1 IN CANCER BIOLOGY: REGULATOR OF EMT, METASTASIS, AND IMMUNE EVASION

MTA1 and EMT in tumor progression

The MTA1 protein has been found to play a significant role in modulating the body's inflammatory responses. It functions as both a target and a component of the NF-κB signaling pathway, which is essential for regulating the body's immune and inflammatory responses. When macrophages, a type of immune cell, are exposed to *Escherichia coli* lipopolysaccharide (LPS), MTA1 is activated through the NF-κB pathway, leading to the activation of inflammatory processes. Studies have demonstrated that the absence of MTA1 impedes the ability of LPS to induce NF-κB signaling and the production of cytokines in macrophages, indicating MTA1's crucial role in inflammatory signaling. Interestingly, MTA1 exhibits dual regulatory functions in the inflammatory response: under normal conditions, it suppresses the expression of certain cytokine genes, but becomes a coactivator of cytokines when macrophages are stimulated by LPS. Furthermore, LPS stimulation of macrophages results in an increased expression of cytokines, and MTA1 is involved in the immediate defense response during cellular injury or infection. This suggests that MTA1 expression is likely induced by extracellular signals that activate the NF-κB signaling pathway. Given that the NF-κB signaling pathway is involved in regulating the expression of both pro- and anti-inflammatory cytokines, MTA1 is suggested to be an upstream modulator of inflammation and the body's immune response. Apart from its role in immediate inflammatory responses [8], MTA1 also plays a critical role in maintaining the balance of inflammatory responses. For example, MTA1 has been found to enhance LPS-induced inflammation by targeting a signaling molecule called MyD88 in stimulated macrophages. In addition, MTA1 regulates local inflammatory responses in specific cells during the development of acute lung injury and in the synovium of individuals with rheumatoid arthritis. These findings underscore the multifaceted role of MTA1 in immune and inflammatory processes (Fig. 2) [9].

MTA1–mediated immune modulation

MTA1 is a protein that plays a key role in altering the behavior of cancer cells, particularly in how they use energy. This is significant because another protein called c-Myc has been strongly linked to reprogramming the metabolism of cancer cells. Recent research has shown that c-Myc and MTA1 together can influence the expression of an enzyme called lactate dehydrogenase A (LDHA). Additionally, there is a protein called JMJD5, which is involved in modifying histones (proteins around which DNA is wound) by removing certain chemical groups from them. JMJD5 has been found to interact with a protein called pyruvate kinase M2 (PKM2) and activate genes involved in the use of sugar in the cell. Interestingly, it has been discovered that MTA1 can increase the

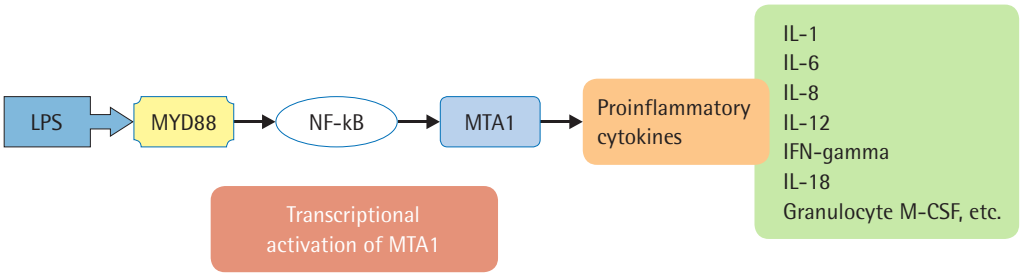

Fig. 2. Transcriptional activation of metastasis-associated protein 1 (MTA1) in inflammation. LPS, lipopolysaccharide; NF-kB, nuclear factor kappa B; IL, interleukin; TNF, tumor necrosis factor; IFN, interferon; M-CSF, macrophage colony-stimulating factor.

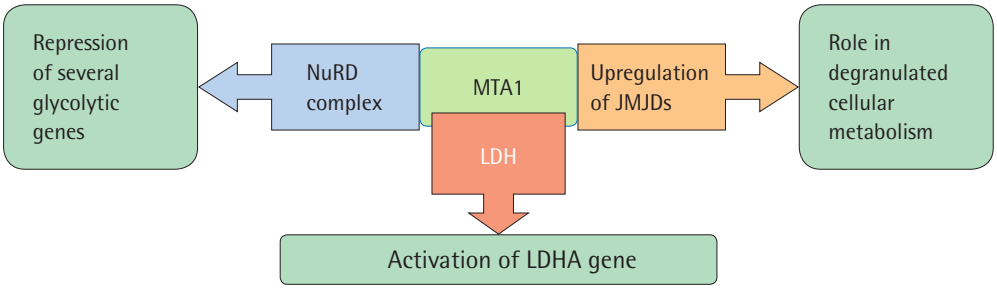

Fig. 3. Activation of LDHA gene in metabolism. MTA1, metastasis-associated protein 1; LDH, lactate dehydrogenase.

expression of JMJD5, raising the possibility that MTA1 may contribute to the disruption of normal cellular metabolism. This fascinating possibility is discussed by Vattem and Pakala (Fig. 3) [10].

MTA1 and cancer metabolism

MTA1 is a protein that plays a significant role in promoting cancer by controlling the expression of genes. It interacts with other proteins to form complexes that can either activate or suppress certain genes. This process can influence various cellular activities involved in cancer development, such as cell growth, blood vessel formation, and the transition of cells from one type to another. This transition allows cancer cells to invade nearby tissues and spread to other parts of the body, a process known as metastasis. MTA1 has been extensively studied in various types of cancer, including breast, lung, colorectal, and prostate cancer (PCa). Research has demonstrated that high levels of MTA1 are often linked to aggressive tumor growth, increased metastasis, and poor prognosis in cancer patients. This suggests that MTA1 plays a crucial role in promoting cancer progression (Fig. 4) [4].

MTA1 EXPRESSION ACROSS CANCER TYPES

Breast cancer

In the context of breast cancer specifically, MTA1 is over expressed in human breast cancer, particularly in tumors with invasive and metastatic characteristics. Studies have shown that breast cancer patients with high levels of MTA1 expression tend to have larger tumors compared to those with low levels of MTA1 expression [11]. Additionally, exosome MTA1, a form of MTA1, may contribute to breast cancer progression by influencing important signaling pathways. This suggests that targeting MTA1 could be a potential therapeutic approach for managing breast cancer [12].

The oncogenic activity of MTA1 is controlled by protein interaction with OGT, OGA, and components of the NuRD complex, which impacts a variety of cellular functions such as colony formation, survival, and proliferation. The MTA1-OGT interaction in breast cancer results in post-translational changes of the serine residues S237, S241, and S246 that help the cells adapt to genotoxic stress. MTA1 protected breast cancer cells by occupying downstream gene promoters under genotoxic stress conditions, which further led to worse dispersion as metastases. By promoting the STAT3, WNT1, MYC, and RAS signaling pathways—all of which are active markers of invasion, transformation, epithelial-mesenchymal transmission, inflammation, and angiogenesis—MTA1 over-expression in carcinoma cells amplifies the consequences of oncogenesis [13].

Lung cancer

Lung cancer is one of the most prevalent and threatening types of cancer, which includes small cell lung cancer (SCLC) and non-

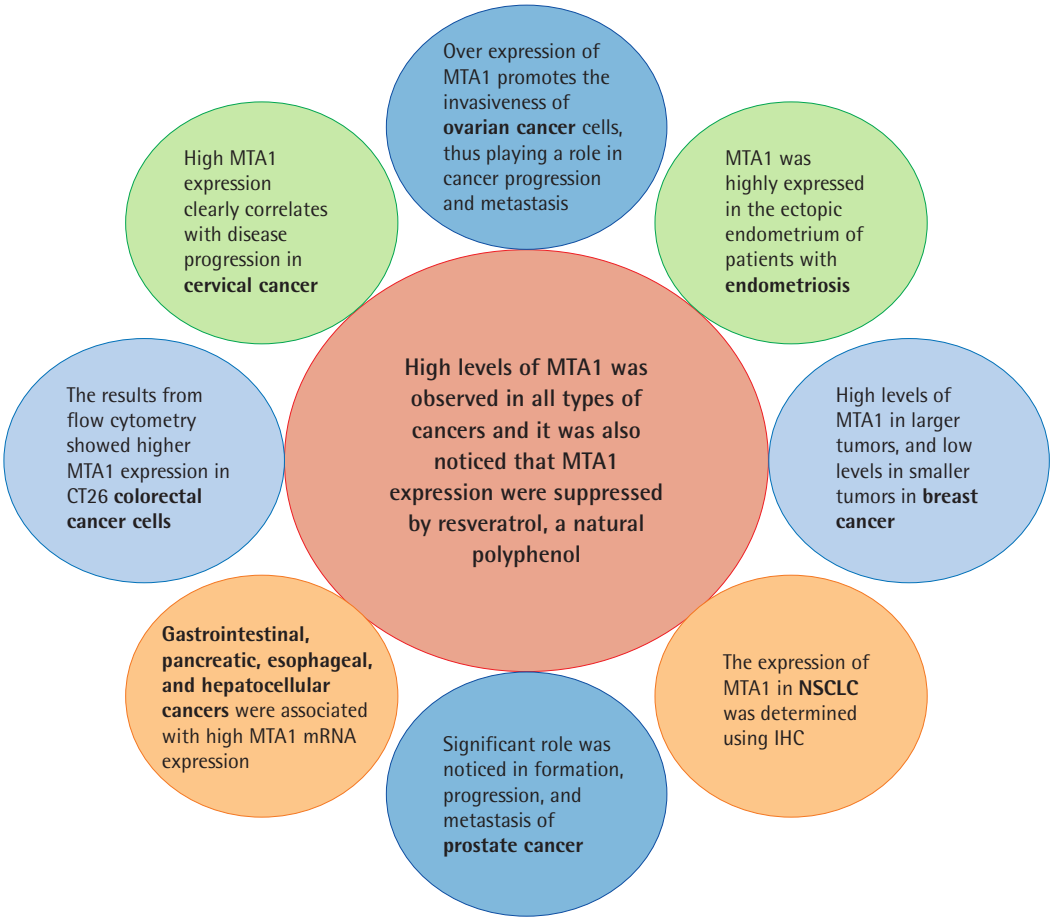

Fig. 4. Role of metastasis-associated protein 1 (MTA1) in all types of cancers. NSCLC, non-small cell lung cancer; IHC, immunohistochemistry.

SCLC (NSCLC). The protein MTA1 is found to be involved in the development and progression of NSCLC in elderly patients and is linked to their prognosis, providing crucial insights for the treatment and outlook of NSCLC [14].

According to a meta-analysis, MTA1 was linked to a bad prognosis for malignancies and was found to be significantly expressed in a number of tumor types, including lung cancer. The macrophages that invade the inside of the tumor are known as tumor-associated macrophages (TAMs). Through a number of mechanisms, TAMs can give tumor cells a special habitat that encourages tumor growth, invasion, and metastasis. In NSCLC, patient survival time was directly correlated with the M1 and M2 macrophage infiltration ratio. Remarkably, both M1/M2 type TAMs were linked to MTA1. For instance, MTA1 can help activate NF-κB signaling to release inflammatory cytokines like interleukin-1β, tumor necrosis factor-α, and macrophage inflammatory protein-2 (MIP2) when LPS activates macrophages (type M1). Loss of PTEN (a negative regulator of AKT) enhanced CCL2 secretion and promoted brain metastases of NSCLC [15].

Prostate cancer

PCa is the most common cancer in men and has become a significant health concern, particularly in Asia. MTA1 has been identified as a key player in the formation, advancement, and spread of PCa, particularly in its metastasis to other parts of the body [16].

MTA1's precise mechanism is unknown, but there is growing evidence that it is directly related to PCa growth, invasion, metastasis, and resistance to treatment. Prostatic intraepithelial neoplasia, or prostatic intraepithelial neoplasia (PIN), is a precancerous lesion of PCa that is defined as an aberrant or heterogeneous proliferation of prostate epithelial tissue, according to multiple studies. By boosting cell survival and proliferation, MTA1 also encourages the transformation of prostate epithelial cells into tumor cells, which results in the formation of PIN. To study the connection between MTA1 and angiogenesis, authors created an MTA1-knockout PCa cell line. Through a series of *ex vivo* experiments, they found that MTA1 promoted angiogenesis through p53 deacetylation or positive regulation of vascular endothelial growth factor (VEGF; key angiogenic protein) expression, which created an en-

vironment that was conducive to PCa tumor growth and potentially supported metastasis. In 2018, a study clarified the function of MTA1 in bone metastasis and PCa progression. They found that MTA1 knockdown led to decreased expression of cathepsin B (CTSB), which in turn led to delayed tumor growth and bone metastasis, as well as decreased colony formation, invasion, and migration of PCa cells. Another study found that in the highly metastatic PCa cell line PC-3M-IE8, siRNA-silenced MTA1 significantly increased E-cadherin expression, which changed cytoskeletal polarity, boosted cell adhesion, and reduced cell invasiveness. The inhibition of phosphorylated AKT significantly changed how MTA1 regulated the expression of E-cadherin. MTA1 controls the p-AKT/E-cadherin pathway, which aids in preventing PCa cells from turning malignant. It identifies the MTA1/EpimiR-22/E-cadherin axis as a novel epigenetic signaling pathway that promotes PCa tumor invasion. A meta-analysis of data from tumor specimens showed a positive correlation between MTA1 and miR-22 levels, indicating that MTA1 and miR-22 inhibit E-cadherin expression [16].

Gastrointestinal cancer

MTA1 is also recognized as a significant factor in gastrointestinal cancers, including gastric, colorectal, esophageal, pancreatic, and liver cancers. Its over-expression has been correlated with the invasiveness and lymph node metastasis of these cancers, underlining its role in their development and progression [8]. Here, we discussed the mechanistic insights of colorectal cancers in association with MTA1 expression.

Colorectal cancer

The level of MTA1 expression and the infiltration of CD8+ T cells are important factors in the body's ability to fight against cancer. CD8+ T cells are immune cells that directly combat tumors. Therefore, it is important to understand how MTA1 expression and its impact on macrophages influence the activation of T cells. Our results from flow cytometry showed that higher MTA1 expression in CT26 colorectal cancer cells increased the production of interferon-gamma (IFN-γ) in T cells, reflecting their activation. Additionally, we looked at immune checkpoints PD-1 and T-cell immunoglobulin in T cells and found that their expression was not significantly different between the groups. However, the presence of macrophages in the culture system significantly increased PD-1 expression and decreased the expression of IFN-γ and T-cell immunoglobulin in T cells. This suggests that macrophages suppress the activation of T cells. It is worth noting that the presence of macrophages decreased the apoptosis (cell death) of T cells in the culture system, especially in the MTA1 knockdown group. We also conducted a T-cell cytotoxicity assay to further analyze the effect of MTA1 expression in colorectal cancer cells on T-cell activity in the tumor environment. We found that macrophages alone did not have a significant effect on cytotoxic tumor cells, but they did enhance the cytotoxic effect of T cells on tumor cells in the culture system. In this system, cancer cells with high MTA1 expression suppressed the ability of T cells to kill tumors, while the presence of additional macrophages increased the cytotoxic effect of T cells on cancer cells. These results suggest that high MTA1 expression in colorectal cancer led to a reduction in the interaction between tumor cells and T cells, and this effect was improved by the presence of classic macrophages. Sadly, the reasons why macrophages were consistently absent in the tumor environment with MTA1 over expression are still unclear. The combined effect of MTA1 over expression ultimately led to a significantly suppressed immune environment [17].

Cervical cancer and ovarian cancer

MTA1 may help cervical cancer cells to spread, move around, stick to surfaces, and grow. Some cervical cancers have high levels of MTA1. When MTA1 is high, the disease tends to get worse, survival rates drop, and cancer cells spread to the lymph nodes. This means the MTA1 gene is an important sign of how aggressive the cancer is and could be a target for future treatments [18].

Abnormal levels of MTA1 expression are linked not only to the development and spread of ovarian cancer but also to its clinical staging. Research has shown that MTA1 expression is significantly elevated in cervical cancer compared to normal cervical tissue, with its upregulation positively correlating with both clinical stage and lymph node metastasis in cervical cancer patients. However, there is a lack of reports regarding MTA1 expression in cervical lesions. Furthermore, MTA1 expression in cervical tissue has been found to be related to the status of high risk-human papillomavirus (HR-HPV) infection. Previous investigations have indicated that MTA1 can interact with the p53 protein. It is hypothesized that the E6 protein from HPV may engage with p53 following HR-HPV infection, leading to a reduction in p53 levels, which in turn may stimulate an increase in MTA1 expression. Additionally, the expression patterns of MTA1 in various cervical lesions were found to align with those of p16 and Ki-67. The upregulation of MTA1 is associated with HR-HPV infection, suggesting that MTA1 could serve as a valuable biomarker for the early detection of cervical lesions [19].

MTA1 makes ovarian cancer cells grow and spread more, rather than just making them grow. When MTA1 is increased, cancer cells become better at moving and invading other tissues. This suggests that high levels of MTA1 help ovarian cancer to grow and

spread, and it is a big part of how the cancer gets more aggressive and spreads to other parts of the body [20].

Endometriosis: a benign disease exhibiting MTA1-mediated EMT

Endometriosis is a benign disease that shares some malignant features. The EMT process plays a key role in the pathogenesis of endometriosis. MTA1 is known to promote EMT and drive various cancers, but its function in endometriosis has not been studied. A study found that MTA1 was highly expressed in the ectopic endometrium of endometriosis patients. MTA1 facilitated the proliferation, migration, and invasion of endometrial stromal cells by inducing EMT. Importantly, these MTA1-driven effects and their expression were suppressed by resveratrol, a natural polyphenol compound. Further investigation in a mouse endometriosis model revealed that MTA1 and the transcription factor ZEB2 were upregulated in ectopic endometrial tissues. Resveratrol was able to inhibit the growth of ectopic lesions and downregulate MTA1 and ZEB2 expression. In summary, MTA1 promotes the EMT process in endometriosis by interacting with ZEB2, and may represent a promising therapeutic target, as its effects can be suppressed by the natural compound resveratrol [21].

Oral cancer

JMJD5 was frequently highly expressed and associated with poor prognosis in oral squamous cell carcinoma. Suppressing JMJD5 markedly reduced cancer cell proliferation, at least partly through the regulation of MTA1 signals. Additionally, silibinin suppressed oral cancer cell proliferation *in vitro*, *in vivo*, and in patient-derived tumor xenografts by downregulating JMJD5 and MTA1. However, the signaling pathway through which silibinin represses JMJD5 and MTA1 in oral cancer cells remains unknown. Nonetheless, silibinin shows potential as a chemotherapeutic agent for oral cancer. This study lays the groundwork for further evaluation of silibinin's mechanism of action and preclinical trials against oral cancer [22].

TARGETING MTA1: THERAPEUTIC POTENTIAL OF NATURAL COMPOUNDS

Resveratrol and derivatives

Pterostilbene (PTER) has the ability to inhibit MTA1 expression and retard tumor growth. PTER downregulates MTA1, decreases the activity and effective concentration of HDAC1, which destabilizes the MTA1/HDAC complex and increases the acetylation and activation of phosphatase and tensin homolog (PTEN) [23]. This inverse relationship between MTA1 and PTEN is significant, as in aggressive PCa, nuclear MTA1 interacts with acetylated PTEN and inhibits its tumor-suppressive functions. Importantly, resveratrol can reactivate PTEN by reversing the negative effect of MTA1/HDAC-mediated deacetylation [24]. A study found that PTER exhibits inhibitory effects in breast, lung, prostate, and esophageal cancers, but less is reported regarding its potential for treating liver cancer. PTER is a type of stilbene compound extracted from sources like grapes, peanuts, and wine [23]. Gnetin C, a resveratrol dimer and dietary compound found in the melinjo plant, is more potent than resveratrol and PTER in exerting anticancer effects in PCa. This potency is, at least in part, due to Gnetin C's inhibition of the cancer-promoting cooperation between MTA1 and ETS proto-oncogene 2 (ETS2). Our data indicate that Gnetin C induces cytotoxicity, cell death, and reduced metastatic ability in PCa cells through MTA1-mediated mechanisms. While the effects of Gnetin C are primarily mediated through MTA1 and the MTA1-dependent inhibition of ETS2, Gnetin C also demonstrated MTA1-independent targeting of ETS2. Therefore, Gnetin C's dual inhibition of the MTA1/ETS2 axis may provide more robust anticancer effects in PCa. Collectively, our findings suggest the potential of Gnetin C as an MTA1/ETS2-targeted chemopreventive and possibly therapeutic strategy for PCa [25].

Emerging MTA1 inhibitors from natural products and drug repurposing

Additionally, other compounds such as isoflavone, gingerol, citronellal, and asiatic acid could be potent MTA inhibitors to prevent cancer metastasis. Furthermore, several structural analogs from

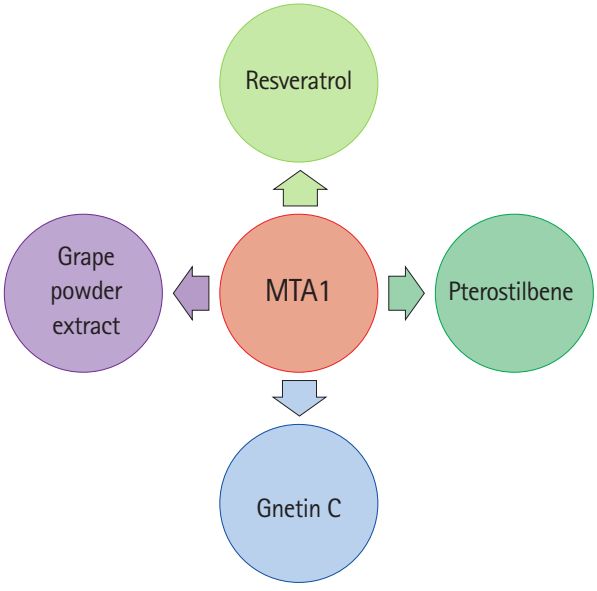

Fig. 5. Inhibitors of metastasis-associated protein 1 (MTA1) in cancer.

DrugBank, including Tramadol, Nabumetone, DGLA, and Hydrocortisone, may be effective and show potency in inhibiting cancer progression in the early stage (Fig. 5) [25].

CONCLUSION

Inhibition of MTA1 is a crucial area of research in the field of cancer biology. Metastasis is the process of cancer cells spreading from the primary tumor site to other parts of the body, leading to the formation of secondary tumors. Therefore, inhibiting MTA1 can potentially prevent or slow down the spread of cancer, making it an attractive target for therapeutic interventions. One approach to inhibiting MTA1 is through the use of small molecule inhibitors. Small molecules are organic compounds that can interact with specific proteins and interfere with their function. Several studies have identified small molecules that can selectively bind to MTA1 and inhibit its activity. These inhibitors can block the interaction between MTA1 and other proteins involved in the metastatic process, thereby reducing the ability of cancer cells to invade and migrate. Inhibition of MTA1 by small molecules has shown promising results in preclinical studies, highlighting its potential as a therapeutic strategy. Another way to inhibit MTA1 is through the modulation of its gene expression. MTA1 expression is regulated by various signaling pathways and transcription factors that control the activity of its gene. Researchers have identified several molecules that can target these pathways and transcription factors to down regulate MTA1 expression. By reducing the production of MTA1 protein, the metastatic potential of cancer cells can be attenuated. This approach offers a more indirect method of inhibiting MTA1 but can still be effective in preventing cancer metastasis. In conclusion, MTA1 represents an exciting druggable target in the field of cancer research. Its association with cancer metastasis and over expression in various types of cancer make it an attractive candidate for therapeutic intervention. Further research and clinical trials are needed to fully understand the therapeutic potential of MTA1 and translate these findings into effective treatments for cancer patients.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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