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Review

MTA1 expression in human cancers – Clinical and pharmacological significance

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ABSTRACT

Remarkably, majority of the cancer deaths are due to metastasis, not because of primary tumors. Metastasis is one of the important hallmarks of cancer. During metastasis invasion of primary tumor cells from the site of origin to a new organ occurs. Metastasis associated proteins (MTAs) are a small family of transcriptional co-regulators that are closely associated with tumor metastasis. These proteins are integral components of nuclear remodeling and deacetylation complex (NuRD). By virtue of being integral components of NuRD, these proteins regulate the gene expression by altering the epigenetic changes such as acetylation and methylation on the target gene chromatin. Among the MTA proteins, MTA1 expression is very closely correlated with the aggressiveness of several cancers that includes breast, liver, colon, pancreas, prostate, blood, esophageal, gastro-intestinal etc. Considering its close association with aggressiveness in human cancers, MTA1 may be considered as a potential therapeutic target for cancer treatment. The recent developments in its crystal structure further strengthened the idea of developing small molecule inhibitors for MTA1. In this review, we discuss the recent trends on the diverse functions of MTA1 and its role in various cancers, with the focus to consider MTA1 as a 'druggable' target in the control of human cancers.

1. Introduction

Cancer is a disease of a mass of mutated cells which undergo uncontrollable cell divisions. As mentioned in the book 'The Emperor of All Melodies-A Biography of Cancer'-by Siddartha Mukharjee, cancer is an uncommited crime. Every year, millions of people around the world die of various cancers. Approximately, 1,685,210 new cases were diagnosed and 595,690 deaths were registered duing 2016 in USA [1]. Remarkably, large number of cancer deaths are due to metastasis, and not because of the primary tumors. Metastasis is therefore one of the important hallmarks of cancer [2]. During metastasis, invasion of primary tumor cells from the site of origin to a new organ occur establishing the malignant tumor at distant location. Size of the tumor appears to be one of the critical factor for tumor metastasis. As the tumor size exceeds 1 cm, these tumor cells tend to metastasize to the secondary sites. Typically, metastasis involves the detachment of primary epithelial cancer cells by loss of E-cadherin, an epithelial marker, resulting in acquisition of mesenchymal phenotype, a process known as epithelial to mesenchymal transition (EMT) [3]. After detaching from the primary tumor through EMT, the disseminated cells enter the blood circulation through cell migration and invasion followed by intravasation. The circulating tumor cells enter the secondary site through extravasation and acclimatizes with the tissue to establish metastasis (Fig. 1). Establishment of secondary tumor is dependent on multiple factors and each primary tumor exibits tissue trophism. For instance, breast tumors are known to metastasize into specific tissues in the order of priority: bone, liver, lung and brain. Given the importance, identification and charactarization of the regulators of tumor metastasis and more importantly, understanding the molecular mechanisms and pathways involved in this critical process is crucial to consider them as

Abbreviations: MTAs, metastasis associated proteins; EMT, epithelial to mesenchymal transition; NuRD, nuclear remodeling and deacetylation complex; HDAC1 or HDAC2, histone deacetylases; MBD, methylated CpG binding domain proteins; RbAb46/48, retinoblastoma associated protein; DOC1, deleted in oral cancer; SAHA, suberoylanilide hydroxamic acid; TSA, trichostatin A; PTER, pterostilbene; E2, estradiol; ERα, estrogen receptor alpha; $Gd@C_{82}(OH)_{22}$, a gadolinium metallofullerenol nanoparticles; SERM, selective estrogen receptor modulators

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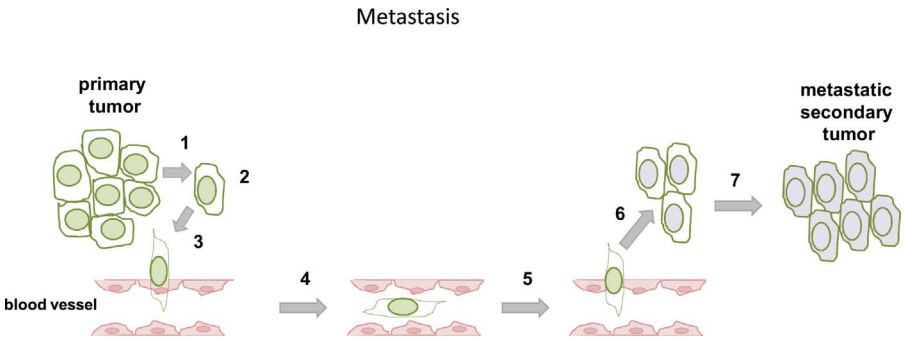

Fig 1. Tumor metastasis. It involves the dissemination of a cancer cell from the primary tumor by 1) epithelial to mesenchymal transition, 2) survival of the cancer cell by exibiting anti-anoikis resistance 3) intravasation of the cancer cell by breaching the nearby blood vessel 4) entering into the circulation 5) extravasation of the cancer cell at the secondary sites 6) acquisition of epithelial phenotypes through mesenchymal to epithelail transition (MET), a reversal of EMT, and 7) colonization at the secondary sites establising the succussful tumor metastasis.

potential targets for controlling cancer. In this review, we consider MTA1 has the potential to be considered as a druggable target in cancers.

2. Identification of MTA1 as tumor associated protein

Since increased mortality and morbidity in cancer patients is primarily due to tumor metastasis, identification and characterization of genes responsible for tumor metastasis is the focus of several laboratories around the world. In 1994, Nicolson laboratory at MD Anderson Cancer Center, USA made such an attempt to identify the metastasis associated genes in breast cancer. This group identified metastasis-associated gene 1 *(MTA1)*, a gene that is harboured on chromosome 14q32.3 in humans, as a differentially expressed gene in highly metastatic 1376NF rat mammary adenocarcinoma system by a differential screening approach [4,5]. Further, increase in the expression of MTA1 was found in metastatic breast cancer [6]. Now it is increasing evident that expression of MTA1 is not only limited to breast cancers, but to several other metastatic tumors that include brain, liver, colon, pancreas, and blood etc [6,7] implying MTA1 as a metastasis specific gene.

Subsequently in 1998, Xue et al. identified MTA1 as a part of Nuclear Remodeling and Deacetylation (NuRD) complex [8,9] creating a paradigm shift in our understanding of MTA1 functions. NuRD is a large protein complex comprising of different subunits, histone deacetylases HDAC1/2, ATP-dependent remodeling enzymes CHD3/4, histone chaperones RbAp46/48, CpG binding proteins MBD2/3, p66α/β and MTA1/2/3 (Fig. 2) [8,9]. The NuRD complex was shown to involve in a variety of physiological and cellular functions [10,11]. As part of NuRD complex, several of these functions have been attributed to MTA1. Since HDACs display deacetylase activity towards histones, deacetylated chromatin interacts with DNA to form closed chromatin resulting in repression of target gene expression [12]. By virtue of this activity, NuRD complex was shown to repress the global gene transcription in a spatio-temporal fashion. Mazumdar et al., for the first time identified the transcription target for MTA1. This study showed that MTA1 is induced by heregulin, a specific ligand for Her-2 receptor in breast cancer cells [13]. Furthermore, MTA1 was shown to interact with ERα in ER-positive breast cancer cells. In light of these observations, MTA1 was predicted to supress ERα-mediated transcription through deacetylation mechanism [13]. Indeed, MTA1 suppressed ERα-target gene expression. Because loss of ERα response is associated with hormone therapy and MTA1 suppresses ERα target gene expression, MTA1 overexpression conferred tamoxifen resistance and exhibited aggressive behavior in breast cancer.

3. NuRD complex – structure and functions

Gene transcription is a tightly regulated molecular process that provides a different RNA repertoire at different developmental stages to perform specific cellular functions. Various chromatin associated protein complexes that perform activities like DNA binding and histone modification are reported to control the gene transcription [14]. The NuRD complex is one such protein complex that regulates the gene transcription through chromatin compaction and decompaction mechanism [15]. It is a 1 MDa multi-subunit protein complex which is highly conserved in eukaryotes and is expressed in a variety of tissues, indicating its essentiality for execution of basic cellular and developmental functions [10,11]. Indeed, NuRD complex has been shown to participate in embryonic development, stem cell maintenance, differentiation, hematopoiesis and many other functions through the general repression of transcription [11,16–20]. Given the importance, understanding its subunit architecture is needed. Recently, the stoichiometry of the different subunits in NuRD complex has been revealed by quantitative mass spectrometry (qMS) method [21]. According to this study, NuRD is composed of one CHD3 or CHD4 protein (chromo domain, helicase, DNA binding domain), one HDAC1 or HDAC2 (histone

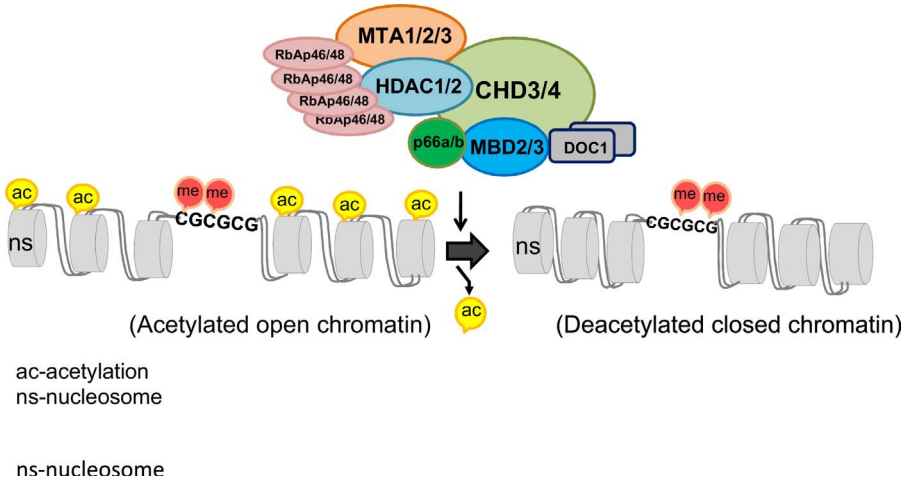

Fig. 2. NuRD complex and its role in chromatin regulation. NURD is a multi-subunit protein complex comprising of different subunits, histone deacetylases HDAC1/2, ATP dependent remodeling enzymes CHD3/4, histone chapron RbAp46/48, CpG binding proteins MBD2/3, p66α/β and specific DNA binding proteins MTA1/2/3. NuRD complex regulate the chromatin and transcription of the target genes by deacetylating the histones. ac, acetylation; me, methylation.