MTA3: A master coregulator of physiology and oncogenesis

The discovery of novel therapeutics for treatment of cancer is today’s prime concern due to abundantly increasing cancer drug resistance and deaths worldwide. MTA3, a member of metastasis-associated protein (MTA) family, plays unique and collaborative roles in cancer including initiation, progression, recurrence, angiogenesis and metastasis. MTA family has six members MTA1, MTA2, MTA3, MTA1s, MTA1-ZG29p, and MTA3L which function as either transcriptional corepressors or coactivators, directly or indirectly affect a wide spectrum of cancer related factors such as Snail, E-cadherin, signal transducer and activator of transcriptions (STATs), and estrogen receptor etc. which help cancer to grow and spread to other organs. MTA3 was originally identified in the year 2001 as an estrogen-dependent component of Mi2/NuRD complex and transcriptional corepressor which negatively regulates genes expression in breast epithelial cells. It is found both in nucleus and cytoplasm.

Fig. 1. A) Structure of MTA3 Protein and B) its interaction in NuRD Transcriptional Complex. MTA3 in NuRD complex binds to the gene promoter and represses or inhibit the expression of Snail, ZEB2 proteins responsible for E-cadherin repression and induction of EMT and metastasis.

MTA3 is a 60 kDa protein expressed by the human MTA3 gene localized in chromosome 2p21.
Structurally, MTA3 gene consists of 20 exons and binding sites to different transcriptional factors including SP1, AP1, and ER in its promoter regions. Currently, seven different MTA3 splicing variants have been reported. The smaller isoform MTA3 (MTA3S) is more abundant at both mRNA and protein levels. MTA3 contains the bromo-adjacent homology domain (BAH domain), which mediates protein-protein interactions; the SANT (SWI, ADA2, NCoR, and TFIIBB) domain important for the formation of Mi2-NuRD complex and the ELM domain responsible for embryonic patterning (Fig. 1). MTA3 interact with DNA and serve as a transcription cofactor by making complex with NuRD.

MTA3 plays crucial role both in physiological and pathological contexts by interacting with many proteins. Infect, MTA3 may act as a tumor suppressor as well as oncogene.

![Fig. 2. Regulatory roles of MTA3 in normal development and cancers.](image)

Under normal expression and physiological conditions MTA3 regulates growth and functions of various tissues and organs. In brain, MTA3 helps in the development of the nervous system, acts as a tumor suppressor and prevents Alzheimer's disease. MTA3 participates in primitive hematopoiesis and prevents hematopoietic and immune disorders. In mammary gland development, MTA3 plays a fundamental role in regulating the differentiation of B Lymphocytes by inhibiting BCL-6 which is a transcriptional repressor and regulates the fate of B lymphocyte. In ovary, depletion of MTA3 suppresses cell proliferation via inhibition of cell cycle progression and blocking M phase entry and thus functions in granulose cell proliferation. In placenta, MTA3 regulates trophoblast function and differentiation during early pregnancy and is involved in some gestational disorders. MTA3 has also been found implicated in embryonic development and stem
cells. Silencing MTA3 during zebra fish embryonic development with antisense morpholinos abolishes primitive hematopoietic lineages and triggers abnormal angiogenesis.

Misexpression of MTA3 may leads to severe physiological and metabolic complication including cancers. MTA3 regulates cell proliferation, apoptosis, and differentiation in cancers by participating in the processes of histone modification and non-codingRNA.

Downregulation of MTA3 tumor Suppressor has been confirmed in diverse cancer types including breast cancer, Gastroesophageal Junction (GEJ) Adenocarcinoma, lymphomas, leukemia, Ovarian and Endometrial Cancers and brain cancer. MTA3 as a regulator represses invasion and metastasis of cancer cells by repressing expression of Snail, a key transcription factor linked to EMT and cancer metastasis. Reduced expression and activity of MTA3 leads to higher expression of Snai1 and subsequently results in loss of cell adhesion molecule E-cadherin, a crucial protein directly involves the regulation of EMT.

Overexpression of MTA3, functioning in oncongenic properties has also been observed in Uterine Non-Endometrioid Carcinomas, Non-Small Cell Lung Cancer (NSCLC) and Chorionic Carcinoma

In conclusion, MTA3 is a versatile regulator in physiological contexts, cancers and other human diseases (Fig. 2). Further exploring the unrecognized aspects of MTA3 will provide novel molecular targets for the better treatment options for different cancers as well as other human disorders.

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