

Gene Section

Review

MTA3 (metastasis associated 1 family, member 3)

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Published in Atlas Database: June 2014

Online updated version : <http://AtlasGeneticsOncology.org/Genes/MTA3ID41445ch2p21.html>
DOI: 10.4267/2042/56299

This article is an update of :

Brüning A, Mylonas I. MTA3 (metastasis associated 1 family, member 3). *Atlas Genet Cytogenet Oncol Haematol* 2011;15(7):567-569.

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Abstract

MTA3 functions as a transcriptional repressor through interacting with histone deacetylases and nucleosome remodelling complexes such as Mi-2/NuRD.

Since MTA3 inhibits expression of SNAIL, a transcriptional repressor of the cell adhesion protein E-cadherin, downregulation of MTA3 was found to be associated with reduced E-cadherin levels and advanced cancer stages. Recent data also revealed upregulation of MTA3 in non-small lung cancer cells and highly aggressive subtypes of endometrial cancer, additionally indicating cancer-promoting effects of MTA3.

Keywords

Metastasis; gene regulation; chromosome remodelling; oestrogen receptor; E-cadherin; B cell

development; cell cycle

Identity

Other names: KIAA1266

HGNC (Hugo): MTA3

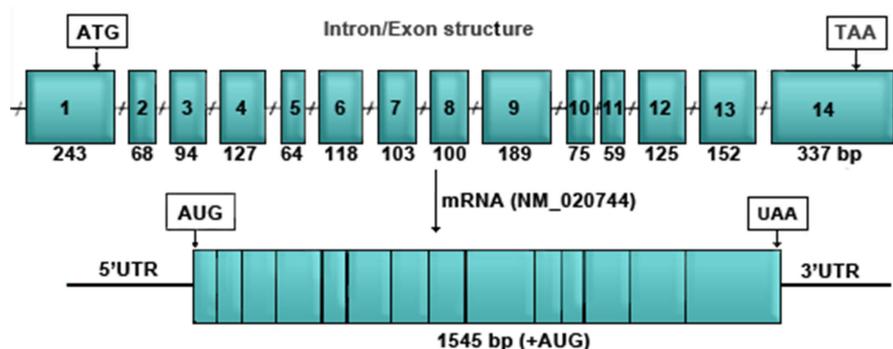
Location: 2p21

DNA/RNA

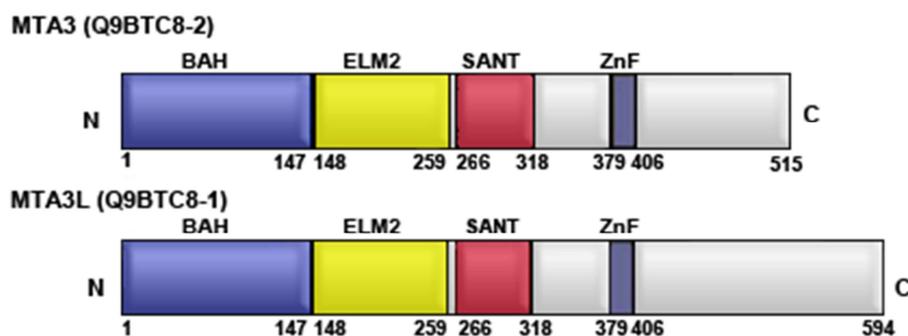
Description

The human MTA3 gene was identified through sequence homologies to other members of the MTA gene family (human MTA1, human MTA2, murine MTA3).

The human MTA3 gene is composed of 14 exons. The MTA3 promoter sequence contains SP1, AP1, and oestrogen receptor binding sites (ER half sites).



Genomic organization of the human MTA3 gene. The intron/exon structure of MTA3 with start (ATG) and stop (TAA) codons indicated. All 14 exons are depicted; the intron sequences shortened for better graphical visualization.



Domain structure of the MTA3 protein. BAH (bromo-adjacent homology) domain: putative protein-protein interaction domain, involved in gene silencing; ELM (Egl-27 and MTA1 homology) domain: unknown function; SANT (SWI3, ADA2, N-CoR and TFIIB B) domain: putative DNA binding domain; ZnF (GATA-type zinc finger) domain: direct DNA binding domain.

Transcription

Two open reading frames of 1785 bp (isoform 1; 594 aa; MTA3L) and 1548 bp (isoform 2; 515 aa; MTA3S, MTA3) were identified and predicted to be transcribed. The smaller isoform (MTA3S = MTA3) appears to be the most abundantly expressed isoform at the RNA and protein level.

Pseudogene

PGO.9606.51655; PGO.9606.72237.

Protein

Description

MTA3 functions as a transcriptional repressor by interacting with histone deacetylases and nucleosome remodelling complexes such as Mi-2/NuRD.

Expression

MTA3 expression has been found in normal human breast, ovarian, lung, and endometrial epithelial cells, in malignant breast, ovarian, lung, and

endometrial cancer cells and cancer cell lines, in trophoblast cells and chorionic cancer cell lines, in germinal centre B cells, and in B cell-derived lymphomas.

A tissue distribution analysis of MTA3 expression in mice revealed a widespread distribution of MTA3 in the developing embryo and in adult tissues (heart, brain, spleen, lung, liver and kidney).

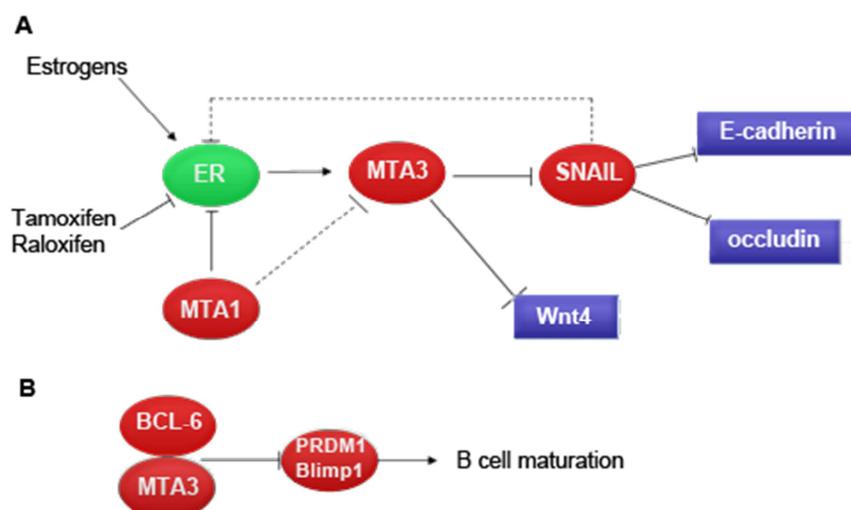
Localisation

MTA3 exhibits primarily a nuclear localisation, although additional cytoplasmic localisation has been described.

Function

In epithelial cells, MTA3 maintains the expression of E-cadherin through the suppression of the E-cadherin inhibitor SNAIL.

Expression of MTA3 is regulated by oestrogens via direct binding of the oestrogen receptor to the MTA3 promoter and is thus involved in the generation and maintenance of oestrogen-dependent epithelia such as the breast ductal epithelium.



The MTA3 regulation network. **A.** Breast ductal epithelia cells; epithelial cancer cells. **B.** Germinal center B lymphocytes; B cell-derived lymphomas. The regulation of MTA3 expression and its target genes by transcriptional activators (green) and transcriptional repressors (red) is shown. ER: oestrogen receptor.

Mammary gland development

Animal experiments revealed involvement of MTA3 expression in mammary gland morphogenesis mediated by the suppression of the Wnt4 signalling pathway and upregulation of epithelial cell adhesion proteins such as E-cadherin. Normal mammary gland development, as confirmed and studied by several knock out and knock in mouse models, relies on the concerted and correct integration of diverse signalling pathways, including the Wnt signalling pathway. Secretion of Wnt factors and their binding by mammary epithelial cells is necessary for correct gland development and its deregulation has been described to be involved in tumorigenesis. MTA3 has been shown to inhibit Wnt4 expression by its transcriptional repression function, causing reduced Wnt4 secretion and subsequent lower beta-catenin levels. Therefore, based on the observations made with transgenic mouse models, expression of MTA3 in mammary epithelial cells has been associated with the inhibition of ductal branching in virgin and pregnant murine mammary glands.

Epithelial cancer

Reduced MTA3 expression in epithelial breast cancer, endometrial cancer, and ovarian cancer is associated with cancer progression by promoting the epithelial-mesenchymal transition (EMT). It is principally believed that reduced expression of MTA3 allows higher expression levels of SNAIL and SLUG, two repressors of metastasis-associated cell adhesion proteins such as E-cadherin and occludin. Conversely, MTA3 expression was found to be elevated in non-small lung cancer and in uterine non-endometrioid cancer, in which a growth-promoting effect of MTA3 overexpression was suggested.

Haemangiogenesis and lymphomagenesis

A high expression level of MTA3 was found in germinal centre B lymphocytes, suggesting an involvement in B cell maturation by direct interaction with BCL6. BCL6 (B-cell lymphoma-6) is a transcriptional repressor that is co-expressed with MTA3 in the germinal centre, where normal B cells proliferate and undergo maturation. BCL6 functions as a transcriptional repressor and suppresses, in cooperation with MTA3, the expression of PRDM1 (Pr domain-containing protein 1), a master regulator of plasma cell differentiation. Overexpression of BCL6 is often observed in lymphomas, especially in large B-cell lymphomas. Thus, the cooperative action of BCL6 together with MTA3 is believed to block differentiation of large B-cell lymphomas, facilitating lymphomagenesis.

Placenta development

A conspicuously high expression level of MTA3 in trophoblast cells and trophoblast tumour cells has

suggested involvement of MTA3 in placenta development and homeostasis. MTA3 expression was found to be elevated in preeclampsia patients and to negatively interfere with hCG (human chorionic gonadotropin) expression.

Homology

MTA3 exhibits a high homology to human MTA1, MTA2, and murine MTA3.

Implicated in

Endometrial cancer

Note

MTA3 expression is significantly reduced in endometrioid adenocarcinomas of poor differentiation, although not associated with patients' survival.

By contrast, in uterine non-endometrioid carcinomas, a highly aggressive subtype of endometrial cancer, MTA3 expression demonstrated a significant association with FIGO surgical stage, lymph node involvement, and lymphovascular space invasion.

In uterine non-endometrioid cancer, MTA3 was also revealed to be a significant independent prognostic parameter, associated with patients' progression-free survival, cause-specific survival, and overall survival.

Ovarian cancer

Note

MTA3 expression is reduced in ovarian cancer with poor differentiation, although not at significant levels.

Breast cancer

Note

Although extensively studied on breast cancer cells and tissues, revealing a close correlation of MTA3 expression with oestrogen receptor expression, no studies have yet shown a direct association of MTA3 expression with clinicopathological parameters in breast cancer.

Lung cancer

Note

MTA3 was found to be upregulated in NSCLC (non-small cell lung cancer) tissues and its overexpression correlated with lymph node status and poor patients' prognosis.

Gastric cancer, oesophageal cancer

Note

In gastroesophageal junction (GEJ) adenocarcinomas, MTA3 expression was found to be reduced in cancer tissues and reduced MTA3 expression correlated with worse overall patients' survival.

Ovary (non-malignant)

Note

Murine ovarian granulosa cells of all follicular stages were shown to express high levels of MTA3. Expression of MTA3 in granulosa cells was also shown to promote cell cycle progression by controlling entry into the M phase.

Placenta

Note

A high expression level of MTA3 was observed in placental trophoblast cells and chorionic carcinoma cells.

In patients with preeclamptic gestational disease, MTA3 expression was found to be downregulated and shown to be involved in human chorionic gonadotropin expression by directly repressing the hCG promoter, leading to dysregulated hCG expression as observed in preeclampsia.

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This article should be referenced as such:

Brüning A, Mylonas I. MTA3 (metastasis associated 1 family, member 3). *Atlas Genet Cytogenet Oncol Haematol*. 2015; 19(2):137-140.
