

Gene Section

Mini Review

MTA3 (metastasis associated 1 family, member 3)

Ansgar Brüning, Ioannis Mylonas

University Hospital Munich, Department of Obstetrics/Gynaecology, Molecular Biology Laboratory, Marchioninistrasse 15, 81377 Munchen, Germany (AB, IM)

Published in Atlas Database: November 2010

Online updated version : <http://AtlasGeneticsOncology.org/Genes/MTA3ID41445ch2p21.html>

DOI: 10.4267/2042/45996

This work is licensed under a Creative Commons Attribution-Noncommercial-No Derivative Works 2.0 France Licence.
© 2011 Atlas of Genetics and Cytogenetics in Oncology and Haematology

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).

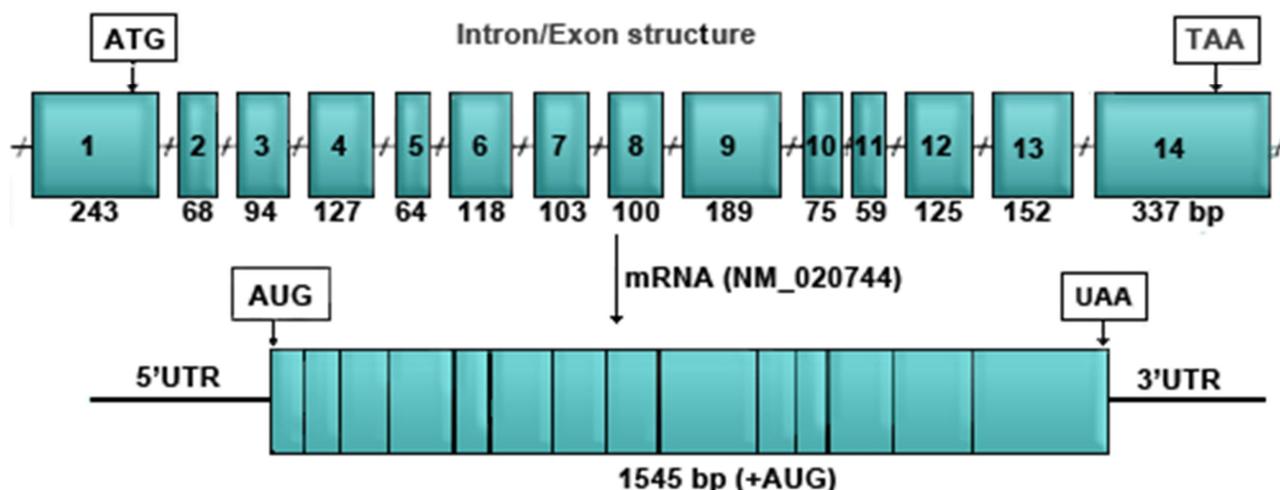
The human MTA3 gene is composed of 14 exons. The MTA3 promoter sequence contains SP1, AP1, and oestrogen receptor binding sites (ER half sites).

Transcription

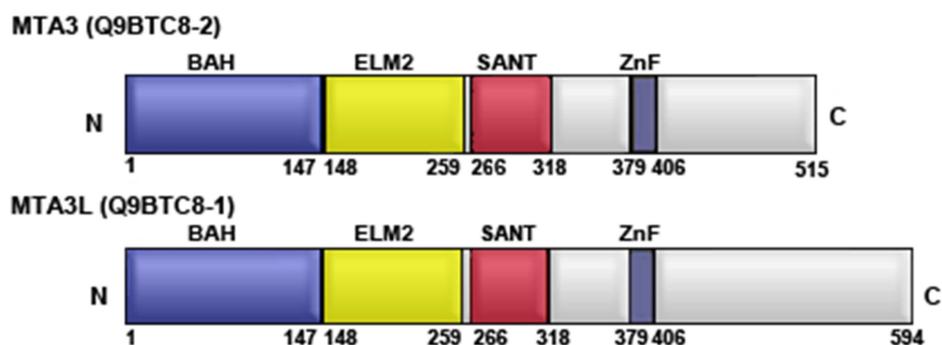
Two open reading frames of 1785 bp (isoform 1; 594 AA; MTA3L) and 1548 bp (isoform 2; 515 AA; MTA3S, MTA3) were identified and predicted to be transcribed. The smaller isoform (MTA3S = MTA3) appears to be the most abundantly expressed isoform at the RNA and protein level.

Pseudogene

PGO.9606.51655; PGO.9606.72237.



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.

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, and endometrial epithelial cells, in malignant breast, ovarian, 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 an even more widespread distribution of MTA3 in the developing embryo and in adult tissues (heart, brain, spleen, lung, liver and kidney). In humans, MTA3 expression appears to be absent from fibroblasts.

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 and the ovarian surface epithelium.

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

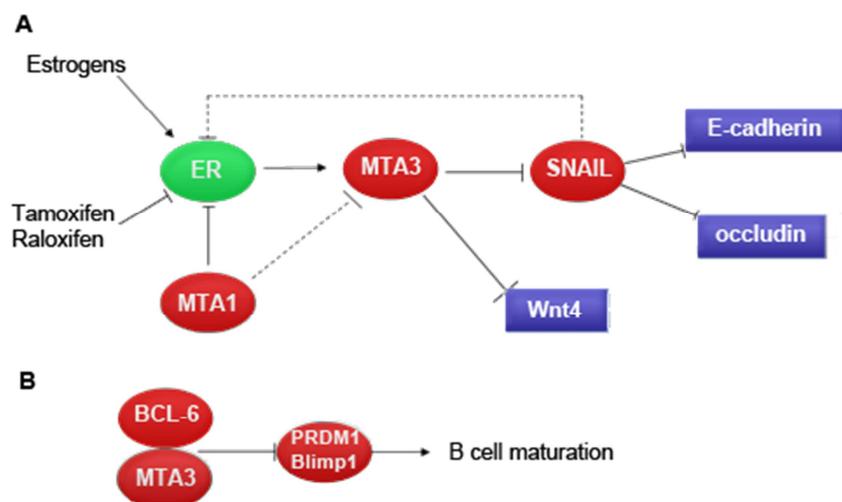
Deregulation of MTA3 expression in epithelial breast cancer, endometrial cancer, and ovarian cancer is associated with cancer progression by promoting the epithelial-mesenchymal transition (EMT). It is principally believed that reduced expression of MTA3 allows higher expression levels of SNAIL and SLUG, two repressors of metastasis-associated cell adhesion proteins such as E-cadherin and occludin.

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 high expression level of MTA3 in trophoblast cells and trophoblast tumour cells suggests



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.

involvement of MTA3 in placenta development and homeostasis. However, the exact role of MTA3 expression for placenta development and the downstream targets of MTA3 in trophoblast cells are unknown and have to be elucidated.

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.

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.

References

Fujita N, Jaye DL, Kajita M, Geigerman C, Moreno CS, Wade PA. MTA3, a Mi-2/NuRD complex subunit, regulates an invasive growth pathway in breast cancer. *Cell*. 2003 Apr 18;113(2):207-19

Fujita N, Jaye DL, Geigerman C, Akyildiz A, Mooney MR, Boss JM, Wade PA. MTA3 and the Mi-2/NuRD complex regulate cell fate during B lymphocyte differentiation. *Cell*. 2004 Oct 1;119(1):75-86

Fujita N, Kajita M, Taysavang P, Wade PA. Hormonal regulation of metastasis-associated protein 3 transcription in breast cancer cells. *Mol Endocrinol*. 2004 Dec;18(12):2937-49

Mishra SK, Talukder AH, Gururaj AE, Yang Z, Singh RR, et al. Upstream determinants of estrogen receptor-alpha regulation of metastatic tumor antigen 3 pathway. *J Biol Chem*. 2004 Jul 30;279(31):32709-15

Zhang H, Singh RR, Talukder AH, Kumar R. Metastatic tumor antigen 3 is a direct corepressor of the Wnt4 pathway. *Genes Dev*. 2006 Nov 1;20(21):2943-8

Zhang H, Stephens LC, Kumar R. Metastasis tumor antigen family proteins during breast cancer progression and metastasis in a reliable mouse model for human breast cancer. *Clin Cancer Res*. 2006 Mar 1;12(5):1479-86

Jaye DL, Iqbal J, Fujita N, Geigerman CM, Li S, et al. The BCL6-associated transcriptional co-repressor, MTA3, is selectively expressed by germinal centre B cells and lymphomas of putative germinal centre derivation. *J Pathol*. 2007 Sep;213(1):106-15

Brüning A, Makovitzky J, Gengelmaier A, Friese K, Mylonas I. The metastasis-associated genes MTA1 and MTA3 are abundantly expressed in human placenta and chorionic carcinoma cells. *Histochem Cell Biol*. 2009 Jul;132(1):33-8

Li X, Jia S, Wang S, Wang Y, Meng A. Mta3-NuRD complex is a master regulator for initiation of primitive hematopoiesis in vertebrate embryos. *Blood*. 2009 Dec 24;114(27):5464-72

Brüning A, Jückstock J, Blankenstein T, Makovitzky J, Kunze S, Mylonas I. The metastasis-associated gene MTA3 is downregulated in advanced endometrioid adenocarcinomas. *Histol Histopathol*. 2010 Nov;25(11):1447-56

This article should be referenced as such:

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