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Gene Section
Review

MAGEA3 (melanoma antigen family A, 3)

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Abstract

In the year 1991 Van der Bruggen P et al. cloned and named MAGE-1 gene that encodes MZ2E antigen, which is expressed in melanoma tissues and cell lines (van der Bruggen et al., 1991).
Since then based on sequence similarity MAGE family has expanded to more than 60 genes (Chomez et al., 2001).
According to their chromosomal location and tissue-specific expression pattern, all the members of this family are categorized into two groups; type I (cancer and testis specific) and type II (ubiquitous) MAGE.
MAGEA sub-family has 12 members starting from MAGEA1 to MAGEA12, among them MAGEA7 is a pseudo-gene (Doyle et al., 2010).
The current review summarizes the information specifically on MAGEA3's DNA/RNA, protein structure, function and where the gene is implicated.

Identity

Other names: CT1.3, HIP8, HYPD, MAGE3, MAGEA6

HGNC (Hugo): MAGEA3

Location: Xq28

Note
MAGEA3 is the third member of MAGEA CT-antigen family. Due to its restricted expression in normal testicular and placental trophoblast cells and aberrant expression in various types of cancer cells, MAGEA3 has drawn paramount attention as an anti-cancer immunotherapy.

DNA/RNA

Description

In human X chromosome; MAGEA3, is clustered in q28 along with other MAGEA sub-family members. The gene consists of three exons and is distributed over 3588 bp (Figure 1).

Transcription

MAGEA3 gets transcribed from the reverse (minus/negative) strand of the DNA. The transcript or m-RNA harbors three exons, but only the 3rd exon contributes to the whole ORF (Figure 1). Three transcript variants have been reported till date.

Protein

Description

The MAGEA3 protein consists of 314 amino acids. The protein has a molecular weight of 34747 Da and pI 4.57. Like other MAGEA family members, it has a conserved MAGE homology domain (MHD; 116 aa - 286 aa) (Sang et al., 2011). Unfortunately, till date no clear functional role has been identified for this domain. The protein has also one MAGE NH_2-terminal and one MAGE COOH-terminal region in its structure (Figure 1). The MAGEA3 protein is 85% and 95% identical to MAGEA2 and MAGEA6, respectively (Atanackovic et al., 2010).

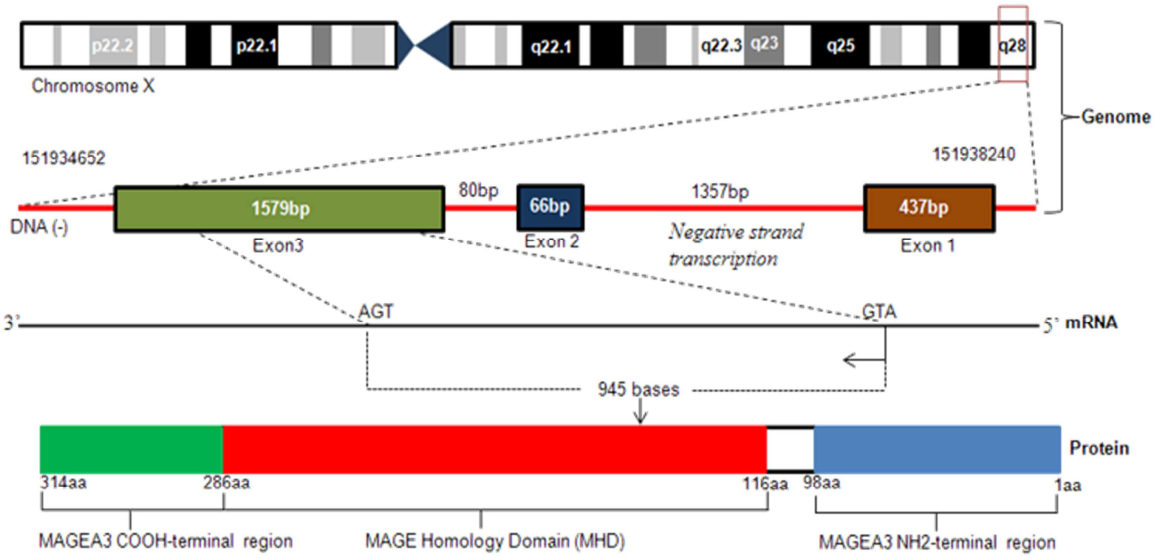

Figure 1. Genomic organization and protein domain structure of MAGEA3.

Expression

The expression of MAGEA3 is restricted to germ cells of testis (primary spermatocytes and spermatogonia) and placental trophoblast, but no other somatic cellular expression have been reported except in wide variety of tumor cells.

Localisation

Cytoplasmic and nuclear expression has been reported (Atanackovic et al., 2010; Barker and Salehi, 2002; Guo et al., 2013).

Function

Since the MAGA3 protein is restricted to germ cell of testis and trophoblast of placenta which are immune privileged tissues, the protein is highly immunogenic and recognized by CTLs when expressed elsewhere.

Its role in spermatogenesis and embryo development is still unknown.

A report says MAGEA3 has the ability to repress p53 function/transactivation, and MAGEA3 knockdown results in increased accumulation of p53 target genes in response to DNA damage (Monte et al., 2006).

Moreover, MAGEA3 directly interacts with and enhances the ubiquitin ligase activity of TRIM28 (a RING E3 ubiquitin ligase) and has a probable role in p53 degradation (Doyle et al., 2010). Its other functional implications in various cancer cells are mentioned in this report. MAGEA family members have significant protein sequence identity, which suggests a functional similarity among them. However, a distinct variability in the regulatory regions of MAGEA genes suggests a possible molecular mechanism of carrying out the same function by different members, under different transcription control.

Regulation

Till now demethylation of promoter region has been reported as the major regulatory mechanism that leads to unusual derepression of MAGEA3 in cancer cells (Figure 2). Histone acetylation is also reported to regulate the expression of MAGEA3 in cancer cells (Kim et al., 2006b; Wischnewski et al., 2006).

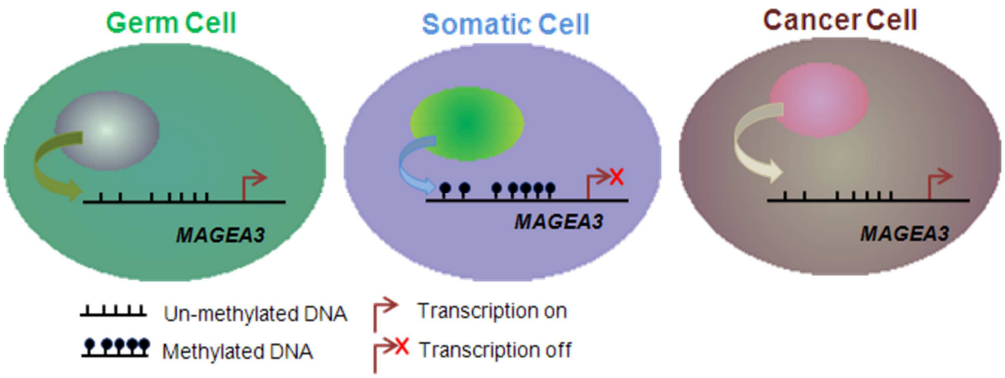

Figure 2. Role of MAGEA3-promoter methylation in spatiotemporal regulation of MAGEA3 gene expression.

The MAGEA3 promoter is found to be hypermethylated in response to FGFR2-IIIb and/or FGF7 stimulating signals resulting into MAGEA3 silencing in MAGEA3-positive thyroid cancer cell lines (Kondo et al., 2007).
MBD1, a methyl-CpG Binding Domain protein is reported to have the ability to bind the unmethylated promoter of MAGEA3 and suppresses the promoter activity that cannot be retracted by Ets-1 transcription factor (Wischnewski et al., 2007).

Homology

Around eight different organisms have orthologs with human MAGEA3.

Implicated in

Various cancers

Note
MAGEA3 expression is being reported in colorectal cancer, breast cancer (10%), bladder cancer (37%), pancreatic cancer (40%), multiple myeloma (41%), gastric cancer (48%), glioma (51.3%), melanoma (65%), thyroid cancer (65%) and NSCLC (85%). Information about MAGEA3 expression and significance in various malignancies is mentioned below.

Pancreatic ductal adenocarcinoma

Note
MAGEA3 expression has been reported in pancreatic cancer cell lines and tissues.
Its expression significantly correlates with poor prognosis in pancreatic cancer patients (Cogdill et al., 2012; Kim et al., 2006a; Kubuschok et al., 2004).

Colorectal cancer

Note
Colorectal cancer cell lines express MAGEA3 and its expression in tumor tissue samples significantly correlates with tumor size (Kim et al., 2006b; Shantha Kumara et al., 2012).

Multiple myeloma

Note
MAGEA3 expression has been detected in multiple myeloma cell lines and patients samples.
Its expression correlates with disease progression i.e. the frequency of expression is higher in relapsed patients than newly diagnosed individuals.
Further, silencing of MAGEA3 induced intrinsic apoptosis pathway in proliferating multiple myeloma cells, which indicates the functional role of MAGEA3 in inhibiting apoptosis of cancer cells (Atanackovic et al., 2010; Nardiello et al., 2011).

Thyroid carcinoma

Note
MAGEA3 expression has been detected in patient tissue samples and its expression was high in the small papillary carcinoma.
Experimental evidences suggest a possible functional role of MAGEA3 in thyroid carcinoma cells' growth, invasion and metastasis (Liu et al., 2008).

Breast cancer

Note
MAGEA3 mRNA expression has been reported in breast cancer patient tissue samples.
Detection of MAGEA3 mRNA in the sentinel lymph nodes (SLN) of breast cancer patients indicates a high chance of micro-metastasis.
It is mostly expressed in the intermediate or poorly differentiated primary breast carcinoma, which is associated with poor prognosis and contributes to higher recurrence rate (Otte et al., 2001; Wascher et al., 2001).

Lung cancer (NSCLC)

Note
MAGEA3 mRNA expression has been reported in lung cancer patient tissue samples.
High level of MAGEA3 is a potential marker for poor prognosis in NSCLC patients (Gure et al., 2005).

Non-Hodgkins lymphoma

Note
MAGEA3 expression has been detected both in cell lines and tissue samples (at RNA level). MAGEA3 in peripheral blood of patients can be a potential tumor marker and is a therapeutic target (Han et al., 2010).

Leukemia

Note
High level of MAGEA3 expression significantly correlates with higher bone marrow blast (Martínez et al., 2007).

Glioma

Note
MAGE3 protein has been detected in glioma tissue samples. Its expression level does not reflect significant difference in overall survival of patients between the pathological grades (Guo et al., 2013).

Gastric cancer

Note
Gastric cancer cell lines express MAGEA3; however, no functional data has been reported till date (Honda et al., 2004).

References

van der Bruggen P, Traversari C, Chomez P, Lurquin C, De Plaen E, Van den Eynde B, Knuth A, Boon T. A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma. Science. 1991 Dec 13;254(5038):1643-7

Chomez P, De Backer O, Bertrand M, De Plaen E, Boon T, Lucas S. An overview of the MAGE gene family with the identification of all human members of the family. Cancer Res. 2001 Jul 15;61(14):5544-51

Otte M, Zafrakas M, Riethdorf L, Pichlmeier U, Löning T, Jänicke F, Pantel K. MAGE-A gene expression pattern in primary breast cancer. Cancer Res. 2001 Sep 15;61(18):6682-7

Wascher RA, Bostick PJ, Huynh KT, Turner R, Qi K, Giuliano AE, Hoon DS. Detection of MAGE-A3 in breast cancer patients' sentinel lymph nodes. Br J Cancer. 2001 Nov 2;85(9):1340-6

Barker PA, Salehi A. The MAGE proteins: emerging roles in cell cycle progression, apoptosis, and neurogenetic disease. J Neurosci Res. 2002 Mar 15;67(6):705-12

Honda T, Tamura G, Waki T, Kawata S, Terashima M, Nishizuka S, Motoyama T. Demethylation of MAGE promoters during gastric cancer progression. Br J Cancer. 2004 Feb 23;90(4):838-43

Kubuschok B, Xie X, Jesnowski R, Preuss KD, Romeike BF, Neumann F, Regitz E, Pistorius G, Schilling M, Scheunemann P, Izbicki JR, Löhr JM, Pfreundschuh M. Expression of cancer testis antigens in pancreatic carcinoma cell lines, pancreatic adenocarcinoma and chronic pancreatitis. Int J Cancer. 2004 Apr 20;109(4):568-75

Gure AO, Chua R, Williamson B, Gonen M, Ferrera CA, Gnjatic S, Ritter G, Simpson AJ, Chen YT, Old LJ, Altorki NK. Cancer-testis genes are coordinately expressed and are markers of poor outcome in non-small cell lung cancer. Clin Cancer Res. 2005 Nov 15;11(22):8055-62

Kim KH, Choi JS, Kim IJ, Ku JL, Park JG. Promoter hypomethylation and reactivation of MAGE-A1 and MAGE-A3 genes in colorectal cancer cell lines and cancer tissues. World J Gastroenterol. 2006a Sep 21;12(35):5651-7

Kim J, Reber HA, Hines OJ, Kazanjian KK, Tran A, Ye X, Amersi FF, Martinez SR, Dry SM, Bilchik AJ, Hoon DS. The clinical significance of MAGEA3 expression in pancreatic cancer. Int J Cancer. 2006b May 1;118(9):2269-75

Monte M, Simonatto M, Peche LY, Bublik DR, Gobessi S, Pierotti MA, Rodolfo M, Schneider C. MAGE-A tumor antigens target p53 transactivation function through histone deacetylase recruitment and confer resistance to chemotherapeutic agents. Proc Natl Acad Sci U S A. 2006 Jul 25;103(30):11160-5

Wischnewski F, Pantel K, Schwarzenbach H. Promoter demethylation and histone acetylation mediate gene expression of MAGE-A1, -A2, -A3, and -A12 in human cancer cells. Mol Cancer Res. 2006 May;4(5):339-49

Kondo T, Zhu X, Asa SL, Ezzat S. The cancer/testis antigen melanoma-associated antigen-A3/A6 is a novel target of fibroblast growth factor receptor 2-IIIb through histone H3 modifications in thyroid cancer. Clin Cancer Res. 2007 Aug 15;13(16):4713-20

Martínez A, Olarte I, Mergold MA, Gutiérrez M, Rozen E, Collazo J, Amancio-Chassin O, Ordóñez RM, Montesinos JJ, Mayani H, McCurdy DK, Ostrosky-Wegman P, Garrido-Guerrero E, Miranda EI. mRNA expression of MAGE-A3 gene in leukemia cells. Leuk Res. 2007 Jan;31(1):33-7

Wischnewski F, Friese O, Pantel K, Schwarzenbach H. Methyl-CpG binding domain proteins and their involvement in the regulation of the MAGE-A1, MAGE-A2, MAGE-A3, and MAGE-A12 gene promoters. Mol Cancer Res. 2007 Jul;5(7):749-59

Liu W, Cheng S, Asa SL, Ezzat S. The melanoma-associated antigen A3 mediates fibronectin-controlled cancer progression and metastasis. Cancer Res. 2008 Oct 1;68(19):8104-12

Atanackovic D, Hildebrandt Y, Jadczak A, Cao Y, Luetkens T, Meyer S, Kobold S, Bartels K, Pabst C, Lajmi N, Gordic M, Stahl T, Zander AR, Bokemeyer C, Kröger N. Cancer-testis antigens MAGE-C1/CT7 and MAGE-A3 promote the survival of multiple myeloma cells. Haematologica. 2010 May;95(5):785-93

Doyle JM, Gao J, Wang J, Yang M, Potts PR. MAGE-RING protein complexes comprise a family of E3 ubiquitin ligases. Mol Cell. 2010 Sep 24;39(6):963-74

Han MH, Eom HS, Park WS, Yun T, Park S, Kim HJ, Jeon CH, Kong SY. Detection of circulating lymphoma cells in patients with non-Hodgkin lymphoma using MAGE-A3 gene expression in peripheral blood. Leuk Res. 2010 Sep;34(9):1127-31

Nardiello T, Jungbluth AA, Mei A, Diliberto M, Huang X, Dabrowski A, Andrade VC, Wasserstrum R, Ely S, Niesvizky R, Pearse R, Coleman M, Jayabalan DS, Bhardwaj N, Old LJ, Chen-Kiang S, Cho HJ. MAGE-A inhibits apoptosis in proliferating myeloma cells through repression of Bax and maintenance of survivin. Clin Cancer Res. 2011 Jul 1;17(13):4309-19

Sang M, Lian Y, Zhou X, Shan B. MAGE-A family: attractive targets for cancer immunotherapy. Vaccine. 2011 Nov 3;29(47):8496-500

Cogdill AP, Frederick DT, Cooper ZA, Garber HR, Ferrone CR, Fiedler A, Rosenberg L, Thayer SP, Warshaw AL, Wargo JA. Targeting the MAGE A3 antigen in pancreatic cancer. Surgery. 2012 Sep;152(3 Suppl 1):S13-8

Shantha Kumara HM, Grieco MJ, Caballero OL, Su T, Ahmed A, Ritter E, Gnjatic S, Cekic V, Old LJ, Simpson AJ, Cordon-Cardo C, Whelan RL. MAGE-A3 is highly expressed in a subset of colorectal cancer patients. Cancer Immun. 2012;12:16

Guo L, Sang M, Liu Q, Fan X, Zhang X, Shan B. The expression and clinical significance of melanoma-associated antigen-A1, -A3 and -A11 in glioma. Oncol Lett. 2013 Jul;6(1):55-62

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