MAGEA3 (melanoma antigen family A, 3)

Biswajit Das, Sujit Suklabaidya, Sumeet Jain, Manas R Baisakh, Shantibhusan Senapati

Institute of Life Sciences, Bhubaneswar, Odisha 751023, India (BD, SS, SJ, SS), Apollo Hospital, Bhubaneswar, Odisha 751003, India (MRB)

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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.

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). MAGEA3 gets transcribed from the reverse (minus/negative) strand of the DNA. The transcript or mRNA 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 NH2-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).

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.
**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).
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


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