Book Chapter

MAGE Genes, The Cancer Tested Antigens Targeted by Immunotherapy

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MAGE Genes: Introduction and Classification

Studying the immune system's ability to recognize and eliminate tumors may help in developing new therapies for cancer. In addition to the known mutated, overexpressed, fused, and oncoviral proteins, male germ cell–specific proteins were added to the list in 1991 when melanoma antigen 1 (MAGE-1) was identified in the melanoma cell line MZ2-MEL. A patient-derived MZ2-MEL cell line was created from a patient (MZ-2) who had, for 10 years, exhibited strong T-cell activity against autologous tumor cells in culture [1]. It is worth mentioning that

a patient survived without disease recurrence for more than 30 years after receiving autologous melanoma cell clones that had been mutagenized in vitro and lethally irradiated. However, all attempts to use MAGE-vaccines clinically have failed. In that sense, MAGE-A3 vaccine trials in Phase III trials were unsuccessful because they did not provide sufficient protection against melanoma, indicating that boosting T-cell responses to the MAGE-A3 protein is not sufficient to hinder the disease progression [2]. Still, MAGE proteins play an important role in tumor biology.

MAGE protein family consists of 10 subfamilies classified into two types based on their gene structures, chromosomal location, and expression patterns in specific tissues (Figure 1). MAGE type I genes (chromosome X-clustered genes), also called cancer-testis antigens (CTAs) are characterized by human leukocyte antigen epitope (HLA) in cancer cells and include MAGE-A, -B, and –C. In addition to cancer cells of diverse origins, germ-line cells in ovaries, testes, and placentas express these genes. However, they are not commonly expressed in adults' tissues [3]. Type II genes are involved in cell proliferation and apoptosis, including MAGE-D, -E, -F, -G, and -H. They are widely expressed in human and murine tissues and are not restricted to cancer tissues**.** In eutherian mammals, the MAGE family, which includes more than 50 related proteins, has expanded to protect the germline from environmental stress and help in stress adaptation. This stress tolerance may explain why MAGEs are abnormally expressed in many cancers where new studies showed a relation between stress and cancer growth [4].

MAGE protein family is a large and highly conserved group of proteins that possess a common domain; 180-amino acid domain known as the MAGE homology domain (MHD). Mammalians share 40% of amino acids in the MHD among all the MAGE subfamilies, but higher conservation is obvious at the subfamily level, where MAGE-D and MAGE-A subfamily members share 75 and 70% MHD residues, respectively. Long-term research into MAGE proteins has not yet revealed their diverse molecular functions. In line with the dynamic nature of the MHD structure, MAGE proteins exert their function through interactions with

diverse proteins. It has been shown that MAGEs cooperate with distinct E3 ligases to regulate ubiquitination of target proteins [5]. E3 ligases are enzymes that recognize and mediate the transfer of activated ubiquitin from the E2 enzyme to a specific target substrate. They are classified into four major classes: RING (really interesting new gene) finger, U- box, PHD finger, and HECT. Efforts were done to identify the function of MAGE proteins and led to a discovery that both type I and II MAGEs bind E3 ubiquitin ligases with RING domains and form MAGE-RING ligases (MRLs). Several distinct MRLs have been subsequently identified. MAGEs recognize and bind their E3 ligase partner through their MHDs [5].

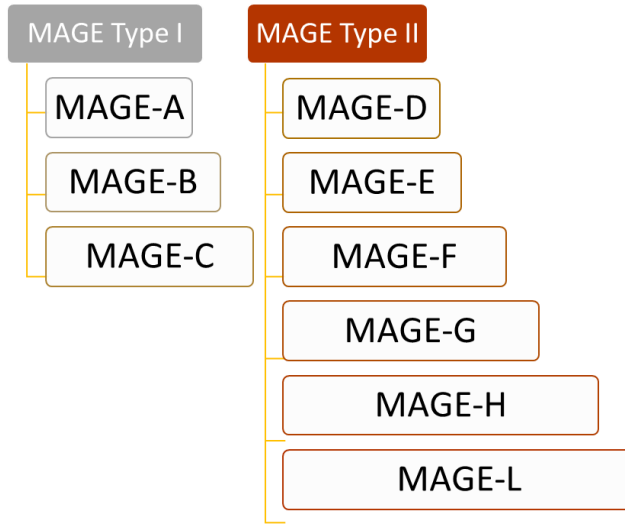

Figure 1: Main members of the MAGE family. Two main classes of MAGE genes, MAGE gene type I and type II which consist of different subfamilies.

Role of MAGE Genes in Cancer

Melanoma-associated antigen (MAGE) family members and specially class I are cancer/testis antigens. They are usually expressed in trophoblasts, germline cells, and a wide range of human cancer types such as melanoma, lung cancer, breast cancer, oral squamous cell carcinoma, esophageal carcinoma, urothelial malignancies and hematopoietic malignancies [6] [7]

[8] [9]. They drive tumor progression through various mechanisms, thereby resulting in tumor growth, metastasis, and recurrence. This common role in tumor progression has drawn research attention into focusing on MAGE's antigenicity and expression pattern in specific tissues to target them with cancer immunotherapy. Despite recent efforts to decipher the epigenetic regulation of certain MAGE family members, the transcriptional programs driving their abnormal expression remain poorly comprehended, and much remains to be discovered. The known tumor-related functions of MAGE family members are summarized in Table1. Additional mechanistical studies concerning MAGE function and regulation will provide some new alternative strategies targeting MAGEs in multiple types of cancers [10].

Table 1: The known tumor-related functions of MAGE family. MAGE genes have been classified as cancer related in various types of tumors with their related biological functions [10].

Type	Subtype	Gene name	Tumor type	Biological functions
MAGE-I	MAGE-A	MAGE-A1	Melanoma, gastric, endometrial, head and neck cancer	- Activating p-C-JUN - Repressing transcription - Recruiting HDAC1
		MAGE-A2	Glioma and breast cancer	- Degrading P53, MDM2 and MDM4 - Increasing ER signaling
		MAGE-A3	Non small lung cancer, hepatocellular carcinoma	- Degrading P53, and AMPKα1 - Enhancing TRIM28-dependent FBP1 degradation
		MAGE-A4	Hepatocellular carcinoma and lung cancer	- Inactivating the oncoprotein gankyrin
		MAGE-A6	Breast, colon, and lung cancer	- Degrading P53, and AMPKα1
		MAGE-A11	Breast cancer, esophageal squamous cell carcinoma, neck and prostate cancer	- Increasing Skp2-mediated degradation of cyclin A and P130 - Decreasing Skp2-mediated degradation of E2F1 - Increasing AR transcriptional activity
		MAGE-A12	Colorectal cancer, prostatic carcinoma , melanoma, bladder, lung, head and neck cancer	- Promoting P21 ubiquitination
	MAGE-C	MAGE-C2	Melanoma, breast, lung and hepatocellular carcinoma	- Enhancing TRIM28-dependent degradation of FBP1 - Inhibiting cyclin E degradation - Increasing KAP1-Ser824 phosphorylation
MAGE-II	MAGE-D	MAGE-D2	Melanoma, gastric, colorectal and hepatocellular carcinoma	- Suppressing TRAIL-induced apoptosis
	MAGE-H	MAGE-H1	Breast and colorectal cancer	- Upregulating mir-200 a/b expression via P73 association

Class I MAGE Genes

Class-I MAGE/cancer testes antigens include the MAGE-A, MAGE-B, and MAGE-C protein families, a group of highly homologous proteins whose expression is repressed in all normal tissues except developing sperm. Aberrant expression of class I MAGE proteins occurs in a wide range of cancer types. Thus, MAGE proteins have long been defined as tumor-specific targets; however, their functions have largely been unknown. Their role in cancer can be explained by the fact that Class I MAGE protein expression may suppress apoptosis by suppressing p53 and may actively contribute to the development of malignancies by promoting tumor survival. Since class I MAGE proteins expression is absent in normal tissues, inhibition of MAGE antigen expression or function represents a novel and specific treatment for melanoma and various malignancies [11].

MAGE-A

MAGE-A belongs to the type I melanoma antigen gene family, and it is associated with different cancer types. MAGE-A1 was the first identified human tumor antigen [12]. It interacts with transcriptional regulator SKIP, which in turn intervenes in signaling pathways involving Notch1-IC and TGF-β. SKIP can act as a transcription activator or repressor, it recruits a repression complex including HDAC. Therefore, MAGE-A1 aids in the setting of gene expression patterns for tumor cell growth [13]. Moreover, MAGE-*A expression is associated with low survival in* lung cancer patients [14], and it was also associated with malignant transformation in leukoplakia which is a precursor of oral and laryngeal squamous cell carcinoma despite the fact that it was not expressed in healthy oral mucosa [15]. MAGEA1-A3 and A12 have been shown to be expressed at an early stage in breast cancer [16].

MAGE-A3 is expressed in bladder cancer and represents a candidate for cancer immunotherapy, where it is thought to have an anti-oncogenic effect through diminishing proliferation and inducing apoptosis by regulating p21 and p53 [17]. MAGE-A4 is overexpressed in various cancers including non-small cell lung

carcinoma and it is widely used for cancer vaccine therapy. It was identified to inhibit apoptosis via caspase-3 and P53 interaction [18]. MAGE-A9 and MAGE-A11 are expressed in breast cancer and their expression was positively associated with estrogen receptors (ER) and HER2 expression [19].

As aforementioned, MAGE proteins proved to bind RING domain-containing proteins through its MHD (Melanoma Homology Domain). E3 ligase is a protein that recruits E2 ubiquitin conjugating enzyme that is linked to ubiquitin, which in turn will transfer the ubiquitin from E2 to a protein targeted for degradation. MAGE-A3/ 6-TRIM28 E3 ubiquitin ligase complex was found to degrade AMPKα1 resulting in downregulating AMPK signaling during tumorigenesis [20].

MAGE-A proteins were found to form complexes with RING domain proteins, such as MAGEA2/C2-TRIM28, MAGE-B18-LNX, and MAGE-G1-NSE1 complexes [21]. The RING domain is a cysteine-rich domain that normally forms a cross-brace structure that typically coordinates two zinc ions. RING domain proteins are proved to be a huge E3 ubiquitin ligase family, which bind to and localize E2 ubiquitin-conjugating enzymes to substrates for ubiquitination [22]. MAGE proteins regulate the ubiquitin ligase activity of RING domain proteins through binding them and acting as scaffold to their substrates.

MAGE-A2, -A3, -A6, and -C2 bound TRIM28 (also known as KAP1, TIF-1beta, or Krip125) were shown to downregulate the tumor suppressor protein p53 [23].

MAGE-B

MAGE-B belongs to type I MAGE genes forming a cluster of four human genes. The coding regions of the *MAGE-B* genes share about 75% nucleotide identity and about 60% identity with those of most *MAGE-A* genes. *MAGE-B2* is the most abundantly expressed member of the *MAGE-B* family. It has been shown to be overexpressed in a wide range of cancer types where it induces tumor growth and progression [24]. MAGE-B genes are expressed with relatively high frequency and specificity in

hepatocellular carcinoma HCC. Most HCC patients with positive expression of at least one member of the MAGE-B or MAGE-A gene family are adequate candidates to receive specific immunotherapy. Frequent co-expression of multiple members of MAGE-B and MAGE-A subfamilies provides the possibility of using polyvalent vaccines to achieve more effective immunotherapeutic results [25]. In light of its elevated expression in cancers, MAGEB2 is an appealing therapeutic target because it generates immunogenic peptides, making the cells susceptible to vaccination therapy in the same manner as MAGE-A genes. This would be particularly crucial in certain tumors that do not express any of the *MAGE-A* genes [26].

MAGE-C

MAGE-C melanoma antigen family belongs to type I MAGE genes. MAGE-C2 and MAGE-C3 have been shown to be cancer-related where MAGE-C2 binds KAP1, a heterochromatin protein that is robustly phosphorylated by ATM at Ser-824 in response to DNA damage. This binding increases the interaction between KAP1 and ATM and as a result increases KAP1 activation. Therefore, MAGE-C2 may enhance tumor growth through the enhancement of DNA damage repair [27].

MAGE-C3 was shown to be a potential prognostic marker and therapeutic target in cancer. It promotes tumor growth by enhancing epithelial-mesenchymal transition and protecting tumors from immune surveillance [28]. MAGE-C3 plays a role in regulating the cytokine secretion of T cells repressing antitumor immunity and protecting cancer cells. Mechanistically, MAGE-C3 fostered IFN-γ signaling and enhanced programmed cell death ligand 1 (PDL1) through binding IFN-γ receptor 1 (IFNGR1) and strengthening the interaction between IFNGR1 and the signal transducer and activator of transcription (STAT1) (Figure 2). Research was conducted to verify the immunosuppressive function of MAGE-C3, demonstrating that MAGE-C3 has a higher tumorigenic potential in immune-competent mice than in immune-deficient nude mice [29].

_MAGE-C2/CT10 promotes the growth of several tumors where it was shown to induce proliferation and metastasis in prostate cancer through the upregulation of c-Myc expression [30]. C-Myc the master regulator gene of cellular metabolism and proliferation.

MAGE- C1/CT7 is involved in the survival of myeloma cells where its knockdown has led to the apoptosis of malignant cells indicating that their expression is crucial for myeloma precursor's survival [31].

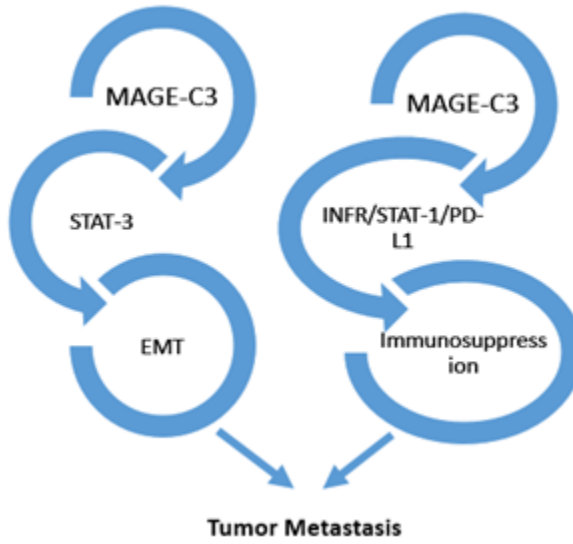

Figure 2: MAGE-C3 role in promotion of tumor metastasis. MAGE-C3 enhances EMT and tumor immunosuppression by activation of PD-L1 through INFR signaling.

MAGE-D2

Melanoma associated antigen D2. The function of MAGE-D2 remained unclear for a long time, but discovering its cellular localization provided the first insights into its biological role [32]. MAGE-D2 plays a role in the regulation, plasma membrane localization and function of the sodium chloride cotransporters SLC12A1 and SLC12A3 in the distal convoluted renal tubule. It

has also been shown that it plays a role in cell cycle regulation. In addition to these functions, MAGE-D2 proved to be closely related to cancer where it induces metastasis and cell adhesion of tumor cells and represents a promising biomarker in gastric tissues for malignancy of GC [33]. A significant subset of human tumors, such as neuroblastoma, breast and melanoma cancer have a low rate of p53 mutations and, thus, presumably, wild type p53 is inactivated via interactions with cellular negative regulators of p53, the p53-dissociators. Studies showed that MAGE-D2 interacts physically with p53 and impairs its transcriptional activity in human cancer cells [34], while a new study proved that MAGE-D2 inhibits MDM2 ligase activity under hypoxia [35]. This will secure P53 from Mdm2 in the presence of MAGE-D2. In that sense, more research should be done to investigate the connection between MAGE-D2 and P53 in malignancies. Furthermore, MAGE-D2 negatively regulates the expression of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) thereby protecting melanoma cells from TRAIL-induced apoptosis [36].

Therapeutic Approach: BiTEs, T cell Engagers Targeting MAGE-A

A therapeutic approach to attack cancer cells through targeting MAGE genes was developed by APO-T. APO-T is a biopharmaceutical company working on the development of new anti-cancer treatments in Netherlands. It is focusing on the development of a bispecific T cell engagers (BiTEs) that target MAGE-A cancer antigen. These engagers will attract the T cells to the cancer cells expressing MAGE-A protein in the tumor environment. Targeting MAGE-A family members specifically is based on their expression in a wide range of cancer types. The fact that MAGE-A is not expressed on the membrane like other cancer markers renders this approach more interesting. This will protect tissues like placenta and testes that express MAGE-A and not MHC-1 from being attacked by these T cell engagers. MAGE-A proteins are degraded by proteasomes and represented on cell surface by human leukocyte antigen as HLA/MAGE derived peptide complex. APO-T BiTEs act as a linker between T cells and cancer cells where it binds CD3 molecule presented

on T cell surface to HLA/MAGE on cancer cell surface. Thus, these engagers only help in the attraction of immune effector cells to cancer microenvironment (Figure3) [36].

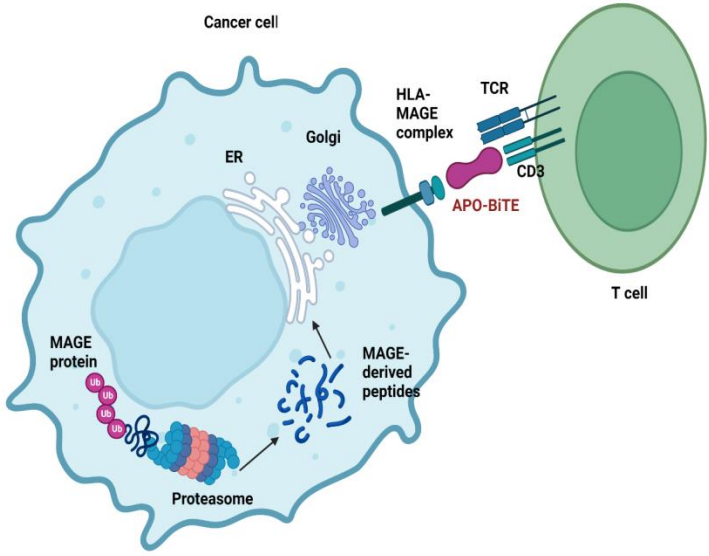

Figure 3: APO-T's BiTEs facilitate removal of cancer cells by immune cells. APO-BITE acts as a bridge between cancer cells and T lymphocytes through binding CD3 molecule to HLA-MAGE complex. Biorender.com

References

1. Whitehurst AW. Cause and Consequence of Cancer/Testis Antigen Activation in Cancer. Annu. Rev. Pharmacol. Toxicol. 2014; 54: 251–272.
2. Daud AI. Negative but not futile: MAGE-A3 immunotherapeutic for melanoma. The Lancet Oncology. 2018; 19: 852–853.
3. P Chomez, O De Backer, M Bertrand, E De Plaen, T Boon, et al. An overview of the MAGE gene family with the identification of all human members of the family. Cancer Res. 2001; 61: 5544–5551.
4. Rebecca R Florke Gee, Helen Chen, Anna K Lee, Christina A Daly, Benjamin A Wilander, et al. Emerging roles of the

MAGE protein family in stress response pathways. Journal of Biological Chemistry. 2020; 295: 16121–16155.
5. Weon JL, Potts PR. The MAGE protein family and cancer. Current Opinion in Cell Biology. 2015; 37: 1–8.
6. Achim A Jungbluth, Scott Ely, Maurizio DiLiberto, Ruben Niesvizky, Barbara Williamson, et al. The cancer-testis antigens CT7 (MAGE-C1) and MAGE-A3/6 are commonly expressed in multiple myeloma and correlate with plasma-cell proliferation. Blood. 2005; 106: 167–174.
7. TS Weiser, G A Ohnmacht, Z S Guo, M R Fischette, G A Chen, et al. Induction of MAGE-3 expression in lung and esophageal cancer cells. The Annals of Thoracic Surgery. 2001; 71: 295–302.
8. Alain Bergeron, Valérie Picard, Hélène LaRue, Francois Harel, Hélène Hovington, et al. High frequency of MAGE-A4 and MAGE-A9 expression in high-risk bladder cancer. Int. J. Cancer. 2009; 125: 1365–1371.
9. Simpson AJG, Caballero OL, Jungbluth A, Chen YT, Old LJ. Cancer/testis antigens, gametogenesis and cancer. Nat Rev Cancer. 2005; 5: 615–625.
10. Lian Y, Meng L, Ding P, Sang M. Epigenetic regulation of MAGE family in human cancer progression-DNA methylation, histone modification, and non-coding RNAs. Clin Epigenet. 2018; 10: 115.
11. Bing Yang, Sean M O'Herrin, Jianqiang Wu, Shannon Reagan-Shaw, Yongsheng Ma, et al. MAGE-A, mMage-b, and MAGE-C Proteins Form Complexes with KAP1 and Suppress p53-Dependent Apoptosis in MAGE-Positive Cell Lines. Cancer Research. 2007; 67: 9954–9962.
12. Zhao J, Wang Y, Mu C, Xu Y, Sang J. MAGEA1 interacts with FBXW7 and regulates ubiquitin ligase-mediated turnover of NICD1 in breast and ovarian cancer cells. Oncogene. 2017; 36: 5023–5034.
13. Laduron S. MAGE-A1 interacts with adaptor SKIP and the deacetylase HDAC1 to repress transcription. Nucleic Acids Research. 2004; 32: 4340–4350.
14. Lina Gu, Meixiang Sang, Danjing Yin, Fei Liu, Yunyan Wu, et al. MAGE-A gene expression in peripheral blood serves as a poor prognostic marker for patients with lung cancer:

MAGE-A related lung cancer prognosis. Thorac Cancer. 2018; 9: 431–438.
15. Christoph A Baran, Abbas Agaimy, Falk Wehrhan, Manuel Weber, Verena Hille, et al. MAGE-A expression in oral and laryngeal leukoplakia predicts malignant transformation. Mod Pathol. 2019; 32: 1068–1081.
16. Ayyoub M, Scarlata CM, Hamaï A, Pignon P, Valmori D. Expression of MAGE-A3/6 in Primary Breast Cancer is Associated With Hormone Receptor Negative Status, High Histologic Grade, and Poor Survival. Journal of Immunotherapy. 2014; 37: 73–76.
17. Zhou G. Expression and function of the tumor antigen MAGE-A3 in bladder cancer cell lines. 2020.
18. Aki Fujiwara-Kuroda, Tatsuya Kato, Takehiro Abiko, Takahiro Tsuchikawa, Noriaki Kyogoku, et al. Prognostic value of MAGEA4 in primary lung cancer depends on subcellular localization and p53 status. Int J Oncol. 2018; 53: 713-724.
19. Shu-Yun Hou, Mei-Xiang Sang, Cui-Zhi Geng, Wei-Hua Liu, Wei-Hua Lü, et al. Expressions of MAGE-A9 and MAGE-A11 in Breast Cancer and their Expression Mechanism. Archives of Medical Research. 2014; 45: 44–51.
20. Carlos T Pineda, Saumya Ramanathan, Klementina Fon Tacer, Jenny L Weon, Malia B Potts, et al. Degradation of AMPK by a Cancer-Specific Ubiquitin Ligase. Cell. 2015; 160: 715–728.
21. Doyle JM, Gao J, Wang J, Yang M, Potts PR. MAGE-RING Protein Complexes Comprise a Family of E3 Ubiquitin Ligases. Molecular Cell. 2010; 39: 963–974.
22. KL Lorick, J P Jensen, S Fang, AM Ong, S Hatakeyama, et al. RING fingers mediate ubiquitin-conjugating enzyme (E2)-dependent ubiquitination. Proc. Natl. Acad. Sci. U.S.A. 1999; 96: 11364–11369.
23. Doyle JM, Gao J, Wang J, Yang M, Potts PR. MAGE-RING Protein Complexes Comprise a Family of E3 Ubiquitin Ligases. Molecular Cell. 2010; 39: 963–974.
24. Rebecca R Florke Gee, Helen Chen, Anna K Lee, Christina A Daly, Benjamin A Wilander, et al. Emerging roles of the

MAGE protein family in stress response pathways. Journal of Biological Chemistry. 2020; 295: 16121–16155.
25. Mou D. Expression of MAGE-B genes in hepatocellular carcinoma. Zhonghua Zhong Liu Za Zhi. 2004; 26: 40–42.
26. Kavita M Pattani, Ethan Soudry, Chad A Glazer, Michael F Ochs, Hao Wang, et al. MAGEB2 is Activated by Promoter Demethylation in Head and Neck Squamous Cell Carcinoma. PLoS ONE. 2012; 7: e45534.
27. Neehar Bhatia, Tony Z Xiao, Kimberly A Rosenthal, Imtiaz A Siddiqui, Saravanan Thiyagarajan, et al. MAGE-C2 Promotes Growth and Tumorigenicity of Melanoma Cells, Phosphorylation of KAP1, and DNA Damage Repair. Journal of Investigative Dermatology. 2013; 133: 759–767.
28. Qingnan Wu, Weimin Zhang, Yan Wang, Qingjie Min, Hongyue Zhang, et al. MAGE-C3 promotes cancer metastasis by inducing epithelial-mesenchymal transition and immunosuppression in esophageal squamous cell carcinoma. Cancer Communications. 2021; 41: 1354–1372.
29. Qingnan Wu, Weimin Zhang, Yan Wang, Qingjie Min, Hongyue Zhang, et al. MAGE-C3 promotes cancer metastasis by inducing epithelial-mesenchymal transition and immunosuppression in esophageal squamous cell carcinoma. Cancer Communications. 2021; 41: 1354–1372.
30. Qiu J, Yang B. MAGE-C2/CT10 promotes growth and metastasis through upregulating c-Myc expression in prostate cancer. Mol Cell Biochem. 2021; 476: 1–10.
31. Djordje Atanackovic, York Hildebrandt, Adam Jadczak, Yanran Cao, Tim Luetkens, et al. Cancer-testis antigens MAGE-C1/CT7 and MAGE-A3 promote the survival of multiple myeloma cells. Haematologica. 2010; 95: 785–793.
32. Céline Pirlot, Marc Thiry, Charlotte Trussart, Emmanuel Di Valentin, Jacques Piette, et al. Melanoma antigen-D2: A nucleolar protein undergoing delocalization during cell cycle and after cellular stress. Biochimica et Biophysica Acta (BBA) - Molecular Cell Research. 2016; 1863: 581–595.
33. Mitsuro Kanda, Shuji Nomoto, Hisaharu Oya, Hideki Takami, Dai Shimizu, et al. The Expression of Melanoma-Associated Antigen D2 Both in Surgically Resected and Serum Samples Serves as Clinically Relevant Biomarker of

Gastric Cancer Progression. Ann Surg Oncol. 2016; 23: 214–221.
34. Rainer Brachmann, Jue Zeng, Robert Culverhouse, Wanghai Zhang, Howard McLeod et al. MAGED2: A novel p53-dissociator. Int J Oncol. 31: 1205-1211.
35. Elie Seaayfan, Sadiq Nasrah, Lea Quell, Maja Kleim, Stefanie Weber, et al. MAGED2 Is Required under Hypoxia for cAMP Signaling by Inhibiting MDM2-Dependent Endocytosis of G-Alpha-S. Cells. 2022; 11: 2546.
36. Hsin-Yi Tseng, Li Hua Chen, Yan Ye, Kwang Hong Tay, Chen Chen Jiang, et al. The melanoma-associated antigen MAGE-D2 suppresses TRAIL receptor 2 and protects against TRAIL-induced apoptosis in human melanoma cells. Carcinogenesis. 2021; 33: 1871–1881.
37. Available online at: https://www.nature.com/biopharmdeal