REVIEW
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The role of the MAGE family: molecular expression, oncogenic roles, and prospects for immunotherapy in cancer

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Author contributions

Niu YT: conceptualization, investigation, statistical analysis, data visualization, and writing the original draft; Bi YT: investigation, statistical analysis, data visualization, and writing the original draft; Zhu L: conceptualization, investigation, writing, review and editing. All authors contributed to the article and approved the submitted version.

Competing interests

The authors declare no conflicts of interest.

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Abbreviations

CTAs, Cancer-Testis Antigens; HCC, hepatocellular carcinoma; MAGE, Melanoma-associated antigen; CpG, CpG dinucleotide; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; HNSC, head and neck squamous cell carcinoma; PPI, protein-protein interaction; EMT, epithelial-mesenchymal transition; DAVID, Database for Annotation, Visualization and Integrated Discovery; FDR, false discovery rate, BRCA, breast cancer; SMC, structural maintenance of chromosomes; COAD, colorectal adenocarcinoma; ER, estrogen receptors; PR, progesterone receptors; PFS, progression-free survival; TCR, T-cell receptor; OV, ovarian cancer; TRIM28, Tripartite Motif Containing 28.

Citation

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Abstract

As a member of the Cancer-Testis Antigens, the Melanoma-associated antigen (MAGE) family is typically expressed in normal tissues such as the testis. However, in various types of tumor cells, their expression is abnormally activated, which is associated with multiple critical processes of tumor cells, including proliferation, apoptosis, immune evasion, DNA damage repair, and metastasis. The abnormal expression of MAGE family genes in multiple cancers and their multifaceted roles in tumor biology have made them an important target in cancer research and treatment. This review comprehensively explores various aspects of the relationship between the MAGE family and cancer, including the molecular characteristics of its members, transcriptional regulation mechanisms, expression patterns in different cancers, phenotypes and oncogenic mechanisms, poor clinical prognosis and potential as targets for immunotherapy. The expression patterns of these genes are closely linked to the clinical features of tumors, providing molecular markers and potential therapeutic targets for the early diagnosis, treatment, and prognostic assessment of cancer.

Keywords: Cancer-Testis Antigens; MAGE family; gene expression; tumor biology; immunotherapy

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Introduction

As one of the causes of premature death in the world, cancer is still a serious threat to human health [1]. Despite ongoing advancements in treatment options, the incidence and mortality rates of malignant tumors continue to rise annually due to the complex interplay of genetic, environmental, and lifestyle factors [2]. In recent years, immunotherapy has become one of the most important treatments for cancer, which is a therapy that utilizes the body's immune system to recognize and attack cancer cells, including monoclonal antibody therapy, modified T-cell therapy, non-specific immunotherapy, and vaccines [3]. Exciting progress in the field of immunotherapy has led to remarkable improvements in the quality of life for cancer patients and has significantly enhanced their overall survival rates [4].

Cancer-Testis Antigens (CTAs) are a class of proteins that have restricted expression in normal somatic cells but are aberrantly expressed in a variety of cancers. CTAs consist of more than 200 members and they can be classified based on their tissue expression patterns into three main categories: Testis Specific, which is exclusively present in the testes; Testis-Brain Specific, which is found in both testes and the central nervous system; and Testis Selective, which are mainly expressed in the testes and at low levels in no more than two additional types of tissues. Furthermore, CTAs can be classified based on their chromosomal location into CT-X genes, located on the X chromosome and often displaying testis-specific expression and higher immunogenicity compared to those on autosomes, such as the MAGE, G Antigen, B Melanoma Antigen, and synovial sarcoma X families. In addition to these, there are Autosomal CTAs, which, despite being located on non-sex chromosomes, are expressed in both tumors and testes [5]. Biological responses to CTAs are mediated through the regulation of transcriptional and post-transcriptional mechanisms and regulate cell proliferation, individuality, and maturation [6]. CTAs can be recognized by cytolytic T lymphocytes in tumor, and play a crucial role in inducing spontaneous immune responses in cancer patients and thus can be one of the targets for immunotherapy [7].

As an antigen-encoding gene identified in melanoma cell lines by T lymphocytes, MAGE-A1 was the first cancer antigen discovered in 1991 [8]. In recent years, an increasing number of genes from the MAGE family have been identified, some of which can be classified as CTAs. These are not only expressed in the testis (and occasionally in the ovaries and placenta) but are also abnormally expressed in cancer [9]. The abnormal activation of MAGE family genes is associated with several key processes of tumor cells, including proliferation, apoptosis, immune evasion, DNA damage repair, and metastasis. Moreover, MAGE family genes are linked to multiple pivotal characteristics of aggressive cancers, such as worsened clinical prognosis, accelerated tumor growth, and metastasis. The expression patterns of these genes are closely intertwined with the clinical features of tumors, offering molecular markers and potential therapeutic targets for the early diagnosis, treatment, and prognostic assessment of cancer. Consequently, MAGE provides a novel avenue for the development of cancer-specific therapies to treat a variety of cancers [10].

Starting from the molecular characteristics of the MAGE family, this review summarizes recent advances in the pathogenesis of different cancers. In addition, we discuss past and current preclinical and clinical studies on immunotherapy targeting the MAGE-A family, with an eye toward possible advancements in MAGE-A-specific immunotherapy (Figure 1).

Molecular attributes and classification of the MAGE family

The diverse proteins of the MAGE family are further subdivided into two groups based on the chromosomal location of their genes [11]. MAGE-I family is expressed solely on the X chromosome and includes three subfamilies: MAGE-A, MAGE-B, and MAGE-C. In contrast, the MAGE-II family is not restricted to the X chromosome and encompasses MAGE-D, MAGE-E, MAGE-F, MAGE-G, MAGE-H, MAGE-L, and Neddin [12]. Members of the MAGE gene family all contain a characteristic sequence composed of 165 to 171 amino acid residues, known as the MAGE Homology Domain [13]. The MAGE Homology Domain is typically situated at the carboxy terminus of the protein and represents a key feature of the proteins encoded by these genes [13]. The MAGE-I family is expressed in normal testicular tissue and is abnormally re-expressed in cancer cells. Due to their unique expression patterns, all MAGE-I genes are classified under the cancer-testis antigen family. The MAGE-A family consists of 12 members, MAGE-A1 to MAGE-A12, with genes mapped to the Xq28 chromosomal region [14]. The MAGE-B family includes 18 members, MAGE-B1 to MAGE-B18, with MAGE-B1 to MAGE-B4 located on chromosome Xq21.2, MAGE-B5, MAGE-B6, MAGE-B10, and MAGE-B18 on chromosome Xp21.3, MAGE-B16 on the Xp21.1 chromosome, and MAGE-B17 on the Xp22.2 chromosome [11, 15, 16]. The MAGE-C family comprises 7 members, MAGE-C1 to MAGE-C7, with MAGE-C1 to MAGE-C3 located on the Xq27.2 chromosome [10, 11, 17] (Figure 2).

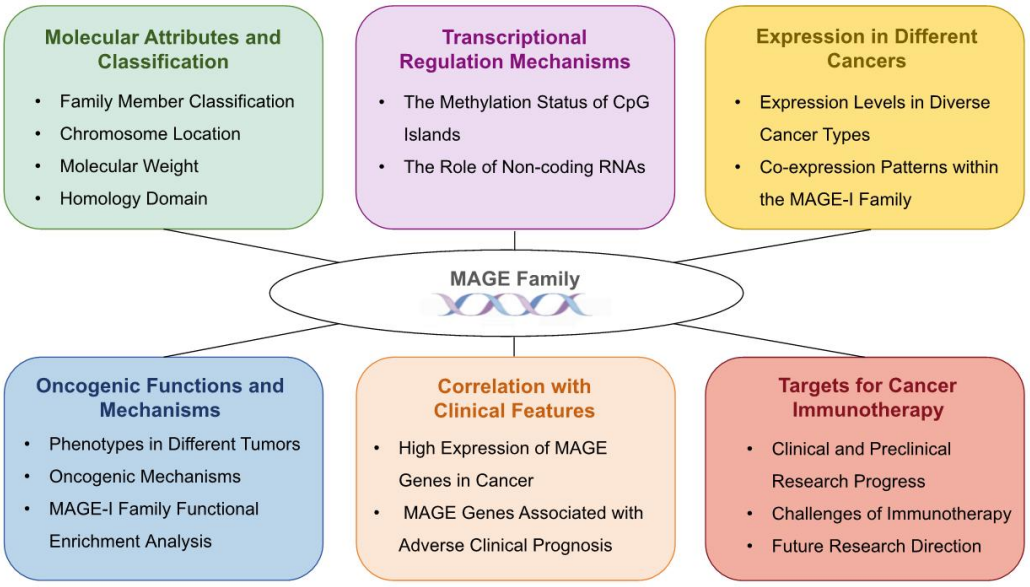


Figure 1 An overview of MAGE family in cancer biology and immunotherapy. CpG, CpG dinucleotide; MAGE, Melanoma-associated antigen.

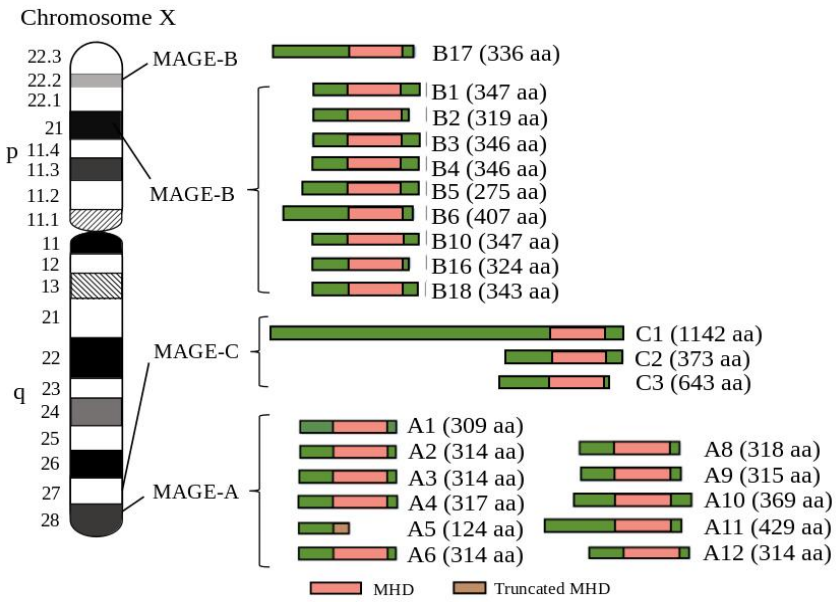


Figure 2 Human MAGE-I family proteins and their known common structural MAGE homology domain [10]. MAGE-A7 (not shown) is a psuedo-gene [18].

Transcriptional regulation mechanisms of MAGE gene expression

The MAGE family constitutes a significant group within CTAs, and like most CTA genes, MAGE genes are predominantly expressed in the testis of normal tissues. They are typically under strict regulatory control in normal tissues, yet they are frequently abnormally activated in tumor cells. Epigenetic regulation appears to play a crucial role in the expression control mechanism of these genes. The transcription start site of MAGE-A1 in somatic cells is rich in CpG sites, and the methylation level of this region is much lower in male germ cells and tumor cells that express the gene compared to somatic cells [19]. Research by Xiao et al. found that in liver cancer cell lines, the expression of MAGE-A1 mRNA is associated with a hypomethylated state of the gene promoter region [20]. Additionally, the findings by Karpf et al. provide another example, demonstrating that in prostate cancer, an increase in MAGE-A11 mRNA expression levels is associated with DNA demethylation and changes in cAMP levels [21]. The promoter region of the MAGE-D4 and MAGE-E1 also contains a high proportion of CpG islands, and demethylation of CpG islands can activate the expression of MAGE-D4 in some cancer cell types, suggesting that the abnormal activation of some MAGE genes in tumor tissues is also closely related to the methylation status of the promoter region [22]. Additionally, Non-coding RNAs have complex and diverse functions, and they can affect multiple aspects of gene expression by binding to target mRNAs. A study conducted in 2011 found that miR-34a can directly target the 3' untranslated region of the MAGE-A gene and reduce the levels of MAGE-A protein [23].

Expression patterns in diverse cancers

Though typically tightly regulated in normal tissues, the MAGE family is frequently activated in tumor cells. The expression of MAGE family members has been particularly scrutinized in melanoma cells. Multiple studies have indicated that while MAGE family members are commonly expressed in cutaneous melanoma, their expression levels are lower in ocular melanoma. Research has found that the mRNA or protein expression levels of MAGE-A1, -A2, -A3, and -A4 in primary cutaneous melanoma can serve as prognostic indicators and are more closely associated with advanced disease stages and distant metastasis [24–27]. Other studies have also shown that the expression rates of MAGE-A1 and MAGE-A4 significantly increase with disease progression, especially in metastatic melanoma [27, 28]. However, in uveal and conjunctival melanoma, the protein and mRNA expression levels of MAGE family members such as MAGE-A1, -A3/6, -A4, and -C1 are found to be low or nearly absent [29, 30].

Furthermore, many MAGE family genes are expressed in lung cancer, especially in non-small cell lung cancer, with varying expression levels among different subtypes. A study from 2018 indicated that MAGE-A1 is predominantly expressed in adenocarcinomas and is more commonly expressed in the elderly and males [31]. Another study found that MAGE-A4 was expressed in 48% of non-small cell lung carcinomas. Ninety percent of lung carcinomas expressing MAGE-A4 were classified as squamous cell carcinomas and 10% were adenocarcinomas [32]. Research by Tsai et al. also showed that MAGE-A6 is differentially expressed in squamous cell carcinoma, while MAGE-B6 and -D4 are differentially expressed in adenocarcinomas [33]. Additionally, MAGE-A1, MAGE-A3, and MAGE-A10 exhibit particularly high mRNA expression levels in primary non-small cell lung cancer [34]. These findings indicate a complex relationship between MAGE family gene expression and lung cancer subtypes, suggesting that members of the MAGE family may be involved in some biological processes in the early stages of lung cancer development.

Extending our focus to hepatocellular carcinoma (HCC), the expression of MAGE family members is also closely associated with tumor progression and prognosis. Research by Mou et al. indicated that MAGE-A1, MAGE-A3, and MAGE-A10 are associated with advanced stages of HCC and tumor size, and patients with persistent positivity for MAGE-A1 and/or MAGE-A3 mRNA are more likely to die from metastasis and/or recurrence, suggesting that these genes may play a role in the disease's progression and metastatic potential [35]. Moreover, MAGE-A1 mRNA expression was detected in 69% of biopsy HCC samples, with higher expression levels in small and well-differentiated HCC, suggesting that MAGE-A1 may be a potential prognostic biomarker for HCC [36].

Beyond melanoma, lung cancer, and liver cancer, which are among the cancers frequently enriched with MAGE family genes, there have been numerous studies on the expression of MAGE family genes in other cancers as well (Table 1). To better understand the expression landscape of MAGE family members in cancer, we have conducted a bioinformatics analysis of the MAGE-I family's expression levels in pan-cancer contexts, complementing our literature review (Figure 3). The analysis focused on the mRNA expression level differences between tumor and normal tissues for the true genes within the MAGE

Table 1 Expression frequency of MAGE family members in different cancer types

Cancer type	MAGE family genes	Frequency	Reference
Non-small cell lung carcinoma	MAGE-A1	TOTAL 46%–50%	[31, 37]
		AD 41%–75%	[34, 37]
		SQ 87%	[37]
	MAGE-A2	TOTAL 88%	[33]
		AD 61%–89%	[33, 38]
		SQ 66%–86%	[33, 38]
	MAGE-A3	TOTAL 45%–80%	[34, 37]
		AD 46%	[37]
		SQ 96%	[37]
	MAGE-A4	TOTAL 35%–48%	[32, 37]
		AD 29%	[37]
		SQ 57%–71%	[33, 37]
	MAGE-A6	AD 11%	[33]
		SQ 36%	[33]
	MAGE-A8	SQ 86%	[33]
	MAGE-A11	TOTAL 79%	[33]
		AD 82%	[33]
		SQ 71%	[33]
	MAGE-B2	TOTAL 69%–80%	[33, 34]
		SQ 79%	[33]
	MAGE-B6	TOTAL 69%	[33]
		AD 80%	[33]
		SQ 43%	[33]
	MAGE-C1	39%–44%	[39, 40]
	MAGE-D2	AD 71%	[33]
	MAGE-D4	AD 66%	[33]
		SQ 29%	[33]
	MAGE-H1	TOTAL 69%	[33]
		AD 71%	[33]
Small cell lung cancer	MAGE-A1	6%	[31]
	MAGE-A2	50%	[38]
HCC	MAGE-A1	43.3%–78%	[35, 36, 41–43]
	MAGE-A3	33.3%–68%	[35, 41, 43]
	MAGE-A8	46%	[41]
	MAGE-C2	20%–34%	[44, 45]
Skin cutaneous melanoma	MAGE-A1	Primary 20%	[27]
		Distant metastasis 9%	[27]
	MAGE-A4	Primary 51%	[27]
		Distant metastasis 44%	[27]
BRCA	MAGE-A3	53%	[46]
Ovarian cancer (OV)	MAGE-A1	56%	[47]
	MAGE-A4	Serous carcinomas 57%	[48]
		Serous tumors of borderline malignancy 9%	[48]
Gastric carcinoma	MAGE-A1	44%	[49]
	MAGE-A3	40%	[49]
	MAGE-A10	80.5%	[50]

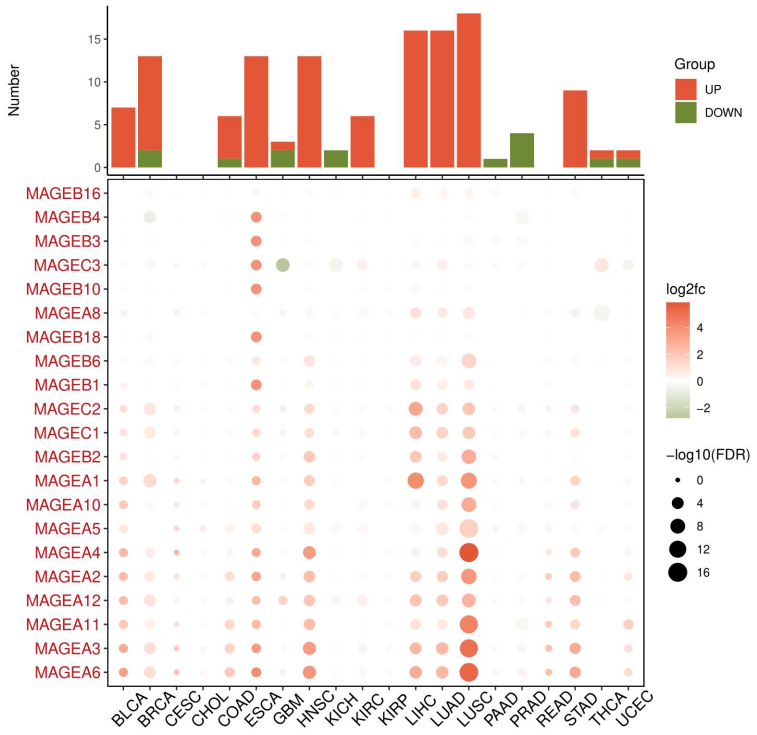


Figure 3 MAGE-I family mRNA expression varies across cancers. The horizontal axis represents various types (normal groups and tumor groups that show no significant statistical differences not displayed on the chart). The vertical axis lists the individual genes of the MAGE-I family. The color of the bubbles indicates the log2 fold change (log2fc) of gene expression, with red representing upregulation and green representing downregulation. The size of the bubbles corresponds to the negative logarithm of the false discovery rate (-log10(false discovery rate, FDR)), where larger bubbles denote lower FDR values, indicating higher statistical significance.

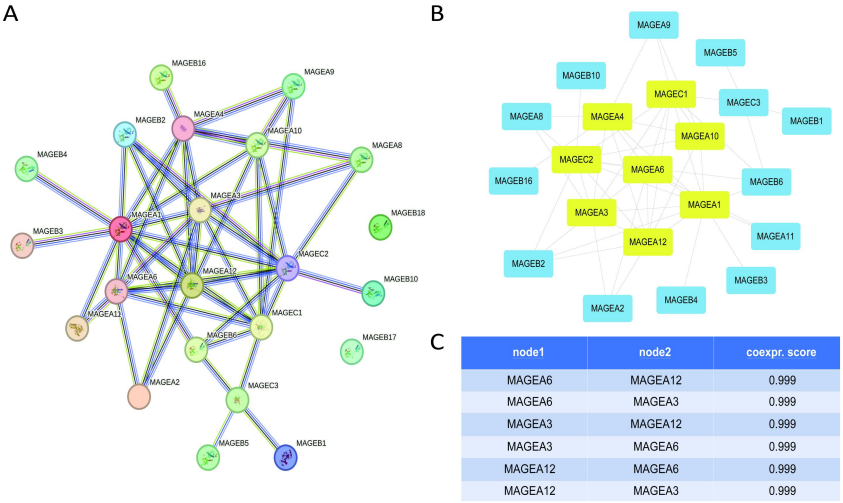
-1 family. The fold change was calculated to generate a bubble chart, which includes cancer types with a sufficient sample size to establish statistically significant differences. The chart illustrates that members of the MAGE-I family exhibit a more pronounced upregulation in certain cancer types, notably lung adenocarcinoma (LUAD), lung squamous cell carcinoma (LUSC), esophageal adenocarcinoma, head and neck squamous cell carcinoma (HNSC), and liver hepatocellular carcinoma. The majority of these genes exhibit an increased expression trend, suggesting a closer association with oncogenic processes within the MAGE-A subfamily. However, it is also observable that some genes demonstrate downregulation in certain cancer types. Some studies have also found that MAGE family genes are downregulated in certain cancers, such as pancreatic cancer, where the expression of MAGE-A1 and MAGE-A3 is infrequent [51, 52]. A study by Serrano et al. found that RT-PCR studies had shown low expression levels of MAGE-A10 in melanoma cell lines, while antibody labeling revealed protein content comparable to that of MAGE-A1. By improving the detection method to address the issue of inefficient PCR primers, they verified that the abundance of MAGE-A10 cDNA is comparable to that of MAGE-A1 [53]. This suggests that detection techniques at the mRNA level may benefit from further optimization, and in some cases, detection at the RNA level alone may not be sufficient to fully assess the role of MAGE family members in cancer, while protein-level detection may provide a more reliable evaluation.

Additionally, to explore the relationships among genes within the MAGE-I family, we constructed their protein-protein interaction network using the STRING online tool (https://cn.string-db.org/) and identified a closely related module within it using the MCODE plugin in Cytoscape. Notably, MAGE-B17 and B18 were found to be isolated from the protein-protein interaction network (Figure 4A), while MAGE-A1, A3, A4, A6, A10, A12, B2, C1, and C2 exhibited a more intimate correlation (Figure 4B). Building on this, we found that the genes MAGE-A3, A6, and A12 showed extremely high co-expression scores, which is consistent with previous research [11, 54].

In summary, the MAGE family genes display a complex expression pattern in cancer. Our comprehensive analysis, including bioinformatics and protein interaction studies, suggests that the aberrant activation of MAGE family genes may play a role in certain biological processes within cancer. Therefore, the oncogenic functions and mechanisms of MAGE family genes merit further attention in cancer research.

The phenotypes and oncogenic mechanisms of the MAGE family in cancer

The MAGE family genes are closely associated with a variety of biological characteristics and functions of tumor cells, with a particularly widespread impact on tumor cell proliferation and apoptosis. For instance, a study by Zhao et al. demonstrated that MAGE-A1 interacts with FBXW7 to regulate the ubiquitin-mediated degradation of NICD1 in the Notch signaling pathway, thereby influencing the proliferation and apoptosis of breast and ovarian cancer cells [55]. Additionally, several studies have shown that MAGE-A3 plays a role in various tumors, such as promoting tumor cell proliferation and chemotherapeutic drug resistance in gastric cancer and enhancing tumor survival in pancreatic cancer by regulating cell cycle and apoptosis signaling pathways [56, 57]. The consistent involvement of MAGE-A3 in these processes raises the possibility that it could be a common factor in tumor progression. A study by Atanackovic D et al. indicated that MAGE-C1/CT7 and MAGE-A3 can promote the survival of multiple myeloma cells, which may be related to their regulation of the apoptosis signaling pathway [58]. Furthermore, the MAGE family genes are also involved in processes such as tumor metastasis and metabolism. A study by Mao et al. pointed out that overexpression of MAGE-A1 significantly increased the proliferation, migration, and invasiveness of LUAD cell lines, and the tumor growth rate was also significantly accelerated [59].



node1	node2	coexpr. score
MAGEA6	MAGEA12	0.999
MAGEA6	MAGEA3	0.999
MAGEA3	MAGEA12	0.999
MAGEA3	MAGEA6	0.999
MAGEA12	MAGEA6	0.999
MAGEA12	MAGEA3	0.999

Figure 4 Protein-protein interaction network of MAGE-I family genes. (A) The protein-protein interaction (PPI) network of the MAGE-I family genes as constructed using the STRING online tool. MAGE-B17 and MAGE-B18 are depicted as isolated nodes within the network, indicating a lack of significant interactions with other MAGE-I family members. (B) Detailed view of a closely related module within the MAGE-I family PPI network, which was identified using the MCODE plugin in Cytoscape. The module includes MAGE-A1, A3, A4, A6, A10, A12, B2, C1, and C2, and it demonstrates a more intricate pattern of interactions. (C) Co-expression Analysis Highlighting the Strong Correlation between MAGE-A3, A6, and A12 Genes.

Members of the MAGE family exert their influence on various aspects of tumorigenesis, including proliferation, metastasis, metabolism, DNA damage repair, and immune evasion, through a multitude of signaling pathways and molecular interactions. Tripartite Motif Containing 28 (TRIM28), also known as KAP1 KRAB-Associated Protein 1 (KAP1) or Transcriptional Intermediary Factor 1-Beta (TIF1-β), is intimately associated with the oncogenic functions of MAGE family members. TRIM28 collaborates with MDM2 to exert E3 ubiquitin ligase activity, particularly in relation to the oncogenic roles of MAGE-A2, -A3, -A6, and -C2 [60]. This collaboration suggests a mechanism by which MAGE family members may modulate cellular processes through the ubiquitin-proteasome system, impacting various aspects of tumor cell behavior. For example, research by Pineda CT et al. has demonstrated that MAGE-A3/6 promotes the ubiquitination of Adenosine 5'-monophosphate (AMP)-activated Protein Kinase alpha (AMPKα1) by binding to TRIM28 and enhancing its E3 ubiquitin ligase activity, leading to a reduction in AMPKα1 protein levels and consequently dampening mammalian target of Rapamycin (mTOR) pathway's activity, which is inhibited by AMPKα1. AMPK promotes the activity of ULK1 by phosphorylating Ser555, whereas mTOR inhibits its activity by phosphorylating Ser757. As ULK1 is a key initiator in the regulation of the autophagy process, the decrease in AMPK protein levels and the concomitant increase in mTOR activity ultimately result in the suppression of autophagy within tumor cells [61]. This suppression of autophagy may contribute to the survival and proliferation of tumor cells. Moreover, the knockdown of MAGE-A6 elevates AMPKα1 protein levels, promoting apoptosis and enhancing the radiosensitivity of non-small cell lung cancer cells [62]. Additionally, Jennifer M. et al. have discovered that both MAGE-A2 and -C2 can bind to TRIM28 to promote the ubiquitination of the tumor suppressor p53 [63]. The ability of MAGE proteins to influence the stability of p53 adds another layer of complexity to their roles in tumorigenesis, as p53 is a critical regulator of cell cycle, apoptosis, cellular senescence, and DNA repair. A study conducted in 2022 revealed that MAGE-C2 inhibits the ubiquitination of p53 by MDM2, while TRIM28 antagonizes this inhibitory effect of MAGE-C2, thus exhibiting a promoting effect on p53 ubiquitination [64]. The interaction between MAGE family members and TRIM28 is also manifested in metabolism and DNA damage repair. The binding of MAGE-A3 and -C2 to TRIM28 facilitates the ubiquitination of Fructose-Bisphosphatase 1 (FBP-1), thereby increasing the Warburg effect [65]. The Warburg effect is a significant characteristic of tumor metabolism, and the promotion of the Warburg effect by members of the MAGE family helps to meet the rapid proliferation demands of tumor cells. MAGE-C2 can also aid in DNA damage repair by promoting the phosphorylation of KAP-1 at serine 824 by the ATM kinase, which is a critical step in the cellular response to DNA double-strand breaks [66]. It is evident that the interaction between TRIM28 and MAGE family members holds significant implications in tumor biology (Figure 5).

Beyond these interactions, MAGE family members can also impact the occurrence and progression of tumors through various other pathways. For instance, MAGE-D1 can induce apoptosis of rat adrenal medullary pheochromoma differentiated cells through the JNK signaling pathway and MAGE-D2 can inhibit autophagy under oxidative stress conditions by ensuring the correct localization of Gas on the plasma membrane and activating the cAMP/PKA signaling pathway, independent of p53 function [20, 67]. MAGE-A4 can influence the mono-ubiquitination of PCNA through interaction with (RAD18 E3 Ubiquitin Protein Ligase (RAD18), thereby participating in the TLS process and DNA damage repair [68]. Regulation of the epithelial-mesenchymal transition (EMT) process to promote tumor migration and invasion is another common mechanism. In esophageal squamous cell carcinoma, MAGE-C3 enhances tumor cell invasion and migration via signal transducer and activator of transcription 3 (STAT3)-mediated EMT and exerts immunosuppressive effects by activating the INF-γ signaling pathway and upregulating PD-1 expression [69]. Research by Gao et al. has shown that the abnormal expression of MAGE-A3 promotes the proliferation, migration, and invasion of cervical cancer cell lines by regulating EMT and activating the Wnt signaling pathway [70].

There is relatively more research on the oncogenic mechanisms associated with the MAGE-I family. To better understand their functions in cancer, a functional enrichment analysis was conducted on the MAGE-I family members using the Database for Annotation, Visualization and Integrated Discovery (DAVID) tool (https://david.ncifcrf.gov/) (Figure 6). Similar to the literature evidence mentioned earlier, some members are enriched in the pathways of positive regulation of ubiquitin-protein transferase activity (MAGE-A2, MAGE-C2) and negative regulation of autophagy (MAGE-A3, MAGE-A6). In addition, all genes are enriched in the nucleus and negatively regulate the transcription process via RNA polymerase II. More than half of the members can affect chromatin accessibility by binding to histone deacetylases, indicating that they are involved in the regulation of gene expression. This is likely one of

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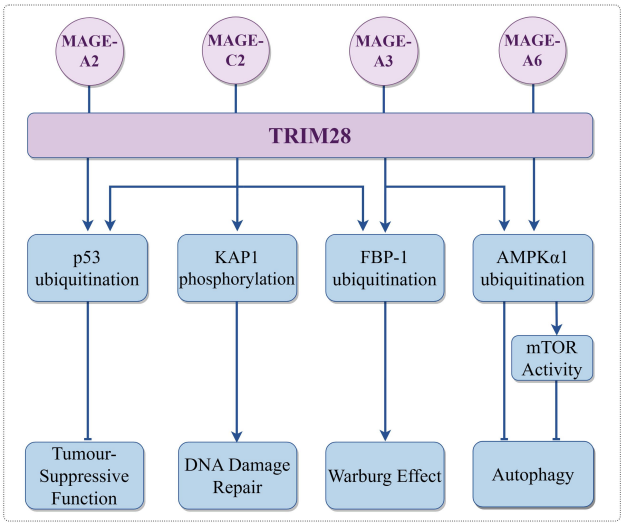

Figure 5 TRIM28 is associated with MAGE Family Proteins in tumors. KAP1, KRAB-Associated Protein 1; FBP-1, Fructose-Bisphosphatase 1; AMPKα, Adenosine 5'-monophosphate (AMP)-activated Protein Kinase alpha; mTOR, mammalian target of Rapamycin.

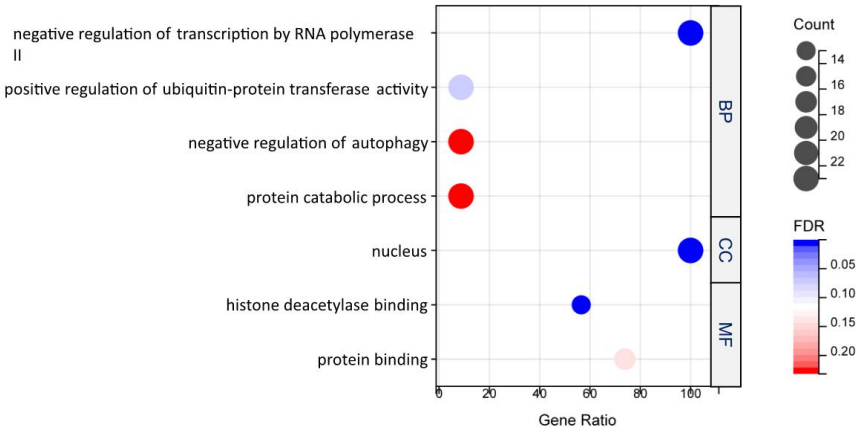

Figure 6 Functional enrichment analysis of MAGE-I family members. Our analysis using the DAVID database identified significant functional enrichment among MAGE-I family members across biological processes (BP), molecular functions (MF), and cellular components (CC). Enriched BP include negative transcriptional regulation, ubiquitin-protein transferase activity regulation, autophagy inhibition and protein catabolic process, while MF highlight and protein binding and histone deacetylases binding. All members are nuclear-localized. Bubble coloration indicates FDR, with blue for low and red for high; bubble size represents the number of enriched genes. BP, biological processes; MF, molecular functions; CC, cellular components; FDR, false discovery rate.

the pathways through which they exert various biological functions. Besides, we utilized the STRING database to construct a protein-protein interaction (PPI) network for KOG4562 (MAGE family member) (Table 2). Bioinformatics analysis revealed connections between KOG4562 and various function-related proteins, including NSE1 (KOG4718), proteins associated with DNA repair (KOG2979), predicted E3 ubiquitin ligases (KOG2177) and Friend of GATA (FOG): Zn-finger (KOG1721). The co-expression relationships between gene sets were further retrieved, including their co-expression scores and highly co-expressed genes. The result showed that these highly co-expressed genes, such as (Non-Structural Maintenance Of Chromosomes Element 1 (NSMCE1), Ring Finger Protein 112 (RNF112), Tripartite Motif Family Like 2 (TRIML2), Zic Family Member 3 (ZIC3), etc., have close interconnections with each other. NSMCE1, as a MAGE-RING E3 ubiquitin ligase, can assemble with MAGE protein, catalyzing the direct transfer of ubiquitin from E2 ubiquitin-conjugating enzyme to specific substrates. ZIC3 is a sequence-specific DNA-binding protein that can bind to the cis-regulatory regions of RNA polymerase II, participating in the regulation of gene expression. Moreover, NSMCE1 is also involved in the maintenance of genomic integrity, DNA damage response, and DNA repair. ZIC3, on the other hand, is a specific DNA-binding protein that can bind to the cis-regulatory regions of RNA polymerase II, participating in the regulation of gene expression. It can be observed that analyses conducted in different ways point to similar pathways, namely ubiquitination, DNA damage repair, and targeted transcriptional regulation of RNA polymerase II.

In summary, the MAGE family genes appear to be multifaceted players in the complex landscape of cancer biology. By integrating these findings, it becomes evident that MAGE family genes are not only involved in the fundamental processes of cell growth and death but also in the more complex behaviors of cancer cells, such as metastasis and adaptation to metabolic changes. This multifaceted involvement suggests that targeting MAGE genes could have a profound impact on cancer treatment strategies, potentially offering a way to disrupt multiple aspects of tumor biology simultaneously.

Correlating MAGE expression with tumor clinical features and prognosis

MAGE genes are not only highly expressed in different cancer types, but bioinformatics analysis and studies have shown that the expression of most MAGE family members is associated with adverse clinical outcomes in various cancers (Figure 7) (Table 3).

In non-small cell lung cancer patients, the expression of MAGE genes is correlated with some adverse clinical features, such as larger tumor volume, pleural invasion, advanced pathological stages, and lymph node metastasis. The positive expression rate of the MAGE-A1 gene ranges from 27% to 46%, the expression positivity rate for the MAGE-A3 gene is relatively high, between 38% and 55%, the positive expression rate for the MAGE-A4 gene is in the range of 19% to 35%, the expression positivity rate for the MAGE-A6 gene is relatively low at 26%, the expression positivity rate for the MAGE-A10 gene is lower, between 14% and 27%, and the expression positivity rate for the MAGE-C1 gene is between 19% and 27% [37, 71, 72]. Among them, the expression of MAGE-A3 has been confirmed as an independent prognostic factor for poor outcomes in lung cancer [37].

For melanoma patients, the positive expression rate of the MAGE-A1 gene in primary tumors ranges from 16% to 20%, which significantly increases to 48% to 51% in metastatic tumors [27, 28]. The positive expression rate for the MAGE-C1 gene in primary tumors is 24%, slightly increasing to 40% in metastatic tumors; the positive expression rate for the MAGE-C2 gene in primary tumors is 33%, and 40% in metastatic tumors [73]. The expression of MAGE-C1 and MAGE-C2 in primary melanoma can serve as a biomarker for predicting lymph node metastasis. Patients with positively expressing primary melanoma have more lymph node metastases, suggesting that the expression of MAGE-A1, MAGE-C1, and MAGE-C2 genes may be related to the invasiveness and metastatic ability of the tumor, thereby affecting patient prognosis.

Besides, in breast cancer patients, the positive expression rate for the MAGE-A1 gene is 6%, for the MAGE-A2 gene it is 19%, the combined positive expression rate for the MAGE-A3 and MAGE-A6 genes is 10% to 15%, for the MAGE-A4 gene it is 13%, and for the MAGE-A12 gene it is 9%. Studies have found that the expression of MAGE-A3/6 is significantly higher in breast cancer tumors that are negative for estrogen receptors (ER) and progesterone receptors (PR), indicating higher invasiveness [74, 75]. Moreover, the expression of MAGE-A3/6 is also associated with a higher histological grade. The positive expression rate for the MAGE-A9 gene reaches 45%, and for the MAGE-A11 gene, it is the highest at 67%. The expression of MAGE-A9 and MAGE-A11 is positively correlated with the expression of Estrogen Receptor (ER) and Human Epidermal growth factor Receptor 2 (HER-2), and a positive status for ER and HER-2 usually indicates a poorer prognosis for the disease. Therefore, the expression of MAGE-A9 and MAGE-A11 is associated with a poor prognosis in breast cancer [76].

Table 2 Protein-protein interaction between KOG4562 and other KEGG orthology groups

Node1	Node2	Node1 annotation	Node2 annotation	Combined score	Co-expression score	Coexpressed, association score		
KOG4562	KOG4718	Uncharacterized conserved protein (tumor-rejection antigen MAGE in humans)	Non-SMC (structural maintenance of chromosomes) element 1 protein (NSE1)	0.870	0.099	MAGE-D2	NSMCE1	0.073
						MAGE-D1	NSMCE1	0.060
						MAGE-F1	NSMCE1	0.050
						MAGE-H1	NSMCE1	0.048
						MAGE-A12	NSMCE1	0.045
KOG4562	KOG2979	Uncharacterized conserved protein (tumor-rejection antigen MAGE in humans)	Protein involved in DNA repair	0.862	0.042	MAGE-F1	NSMCE2	0.062
						MAGE-A1	NSMCE2	0.047
						MAGE-A12	NSMCE2	0.044
						MAGE-A10	NSMCE2	0.042
						MAGE-H1	NSMCE2	0.042
KOG4562	KOG2177	Uncharacterized conserved protein (tumor-rejection antigen MAGE in humans)	Predicted E3 ubiquitin ligase	0.808	0.104	MAGE-E2	RNF112	0.169
						MAGE-E2	MOG	0.141
						MAGE-A10	TRIML2	0.131
						MAGE-C1	TRIML2	0.128
						MAGE-D1	MID1	0.128
						MAGE-C2	TRIML2	0.126
						MAGE-A12	TRIML2	0.122
						MAGE-E1	RNF112	0.109
						MAGE-A3	TRIM51	0.106
KOG4562	KOG1721	Uncharacterized conserved protein (tumor-rejection antigen MAGE in humans)	FOG: Zn-finger	0.795	0.428	MAGE-B18	FAM9A	0.250
						MAGE-C1	ZIC3	0.242
						MAGE-C2	ZIC3	0.242
						MAGE-A10	ZIC3	0.213
						MAGE-B18	ZIM3	0.180
						MAGE-A4	ZIC3	0.177
						MAGE-A10	CTCFL	0.162
						MAGE-C3	ZNF81	0.162
						MAGE-A1	CTCFL	0.140
						MAGE-C2	CTCFL	0.139

Table 3 Correlation between MAGE gene expression and tumor clinical features and prognosis

Cancer type	MAGE family genes	Correlation between expression and clinical features	Reference
Non-Small Cell Lung Carcinoma	MAGE-A1	Larger tumor volume, pleural invasion, advanced pathological stages, lymph node metastasis	[37, 71, 72]
	MAGE-A3	Expression is an independent prognostic factor associated with poor outcomes	[37]
	MAGE-A4	Expression correlates with advanced pathological stages, lymph node metastasis	[37, 71, 72]
	MAGE-A6	Relatively low expression rate	[37, 71, 72]
	MAGE-A10	Lower expression rate	[37, 71, 72]
	MAGE-C1	Lower expression rate	[37, 71, 72]
Melanoma	MAGE-A1	Primary tumor expression 16–20% Metastatic tumor expression 48–51%	[27, 28]
	MAGE-C1	Primary tumor expression 24% Metastatic tumor expression 40%	[73]
	MAGE-C2	Primary tumor expression 33% Metastatic tumor expression 40%	[73]
Breast cancer	MAGE-A1	Expression rate 6%	[74, 77]
	MAGE-A2	Expression rate 19%	[74, 77]
	MAGE-A3/6	Associated with higher invasiveness in breast cancer tumors that are negative for ER and PR	[74, 77]
	MAGE-A9	Expression rate 45%	[76]
	MAGE-A11	Expression rate 67%, positively correlated with ER and HER-2 expression, usually indicating poorer prognosis	[76]
Ovarian cancer	MAGE-A1	Expression rate 15%–53%	[78, 79]
	MAGE-A3	Expression rate 36%–37%	[78, 79]
	MAGE-A4	Expression rate 47%	[78, 79]
Ovarian cancer	MAGE-A9	Expression rate 37%, significantly associated with FIGO staging, high histological grade, CA-125 levels, metastasis	[79]
	MAGE-A10	Expression rate 52%, associated with poorer progression-free survival (PFS)	[78, 79]
Colorectal cancer	MAGE-A1	Expression rate 12%–30%	[80, 81]
	MAGE-A2	Expression rate 28%	[80, 81]
	MAGE-A3	Expression rate 20%–27%	[80, 81]
	MAGE-A4	Expression rate 22%	[80, 81]
Multiple myeloma	MAGE-A1	Expression rate less than 20% in newly diagnosed patients	[82, 83]
	MAGE-A2	Expression rate 36%	[82, 83]
	MAGE-A3/6	Expression rate 37%–41%	[82, 83]
	MAGE-C1	Expression rate 77%, associated with increased plasma cell proliferation index	[82, 83]
	MAGE-C2	Expression rate 50%–59%	[82, 83]
Ovarian cancer	MAGE-A9	Expression rate 37%, significantly associated with FIGO staging, high histological grade, CA–125 levels, metastasis	[79]
	MAGE-A10	Expression rate 52%, associated with poorer PFS	[78, 79]
Colorectal cancer	MAGE-A1	Expression rate 12%–30%	[80, 81]
	MAGE-A2	Expression rate 28%	[80, 81]

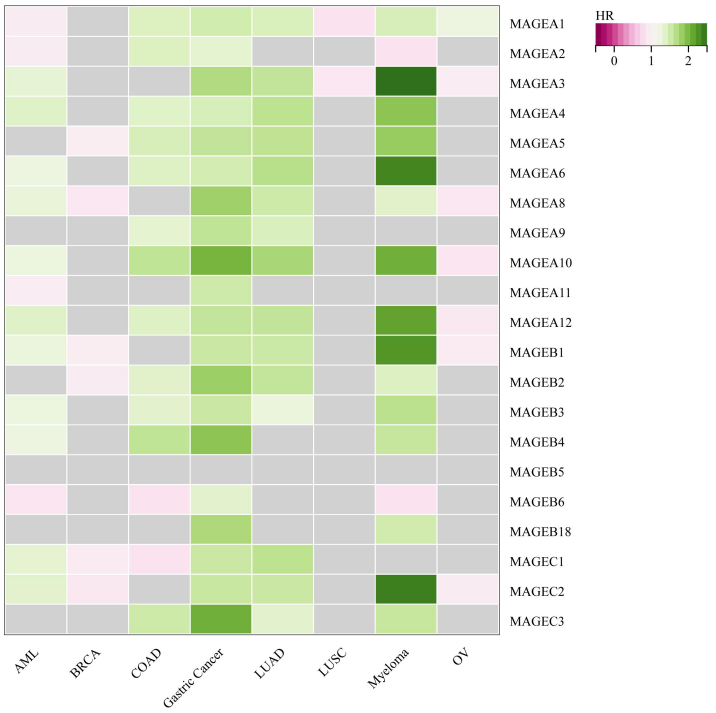

Figure 7 Survival analysis of MAGE-I family members. The survival analysis of MAGE-I family members was conducted utilizing an online Kaplan-Meier tool, with statistical significance set at $P \leq 0.05$ (non-significant $P > 0.05$ are indicated in grey). The heatmap displays hazard ratios (HR) across various cancer types, with HR = 1 marked in white, HR > 1 in green, and HR < 1 in magenta, reflecting the relative risk associated with the expression of these genes. AML, Acute Myeloid Leukemia; BRCA, breast cancer; COAD, colorectal adenocarcinoma; LUAD, lung adenocarcinoma; LUSC, lung squamous cell carcinoma; OV, ovarian cancer; HR, hazard ratios.

For patients with ovarian cancer, the positive expression rate for the MAGE-A1 gene varies widely, ranging from 15% to 53%, for the MAGE-A3 gene it is 36% to 37%, for the MAGE-A4 gene it is 47%, for the MAGE-A10 gene it is 52%, and for the MAGE-C1 gene it is 16% [78, 79]. The expression of MAGE-A1 and MAGE-A10 is associated with poorer PFS and is closely related to a poor prognosis. The positive expression rate for the MAGE-A9 gene is 37%, and the protein expression of MAGE-A9 is significantly associated with FIGO staging, high histological grade, CA-125 levels, and metastasis, all of which are features associated with a poorer prognosis [79].

In patients with colorectal cancer, the positive expression rate for the MAGE-A1 gene ranges from 12% to 30%, for the MAGE-A2 gene it is 28%, for the MAGE-A3 gene it is 20% to 27%, and for the MAGE-A4 gene it is 22%. The expression of MAGE genes is more common in patients with liver metastasis from colorectal cancer, suggesting that the expression of MAGE genes may be related to the metastatic ability of colorectal cancer, thus affecting patient prognosis [80, 81].

It is worth mentioning that the positive expression rate of the MAGE gene is also different in new patients with multiple myeloma and recurrent patients. In patients with newly diagnosed multiple myeloma, the positive expression rate for the MAGE-A1 gene is less than 20% for the MAGE-A2 gene it is 36%, for the MAGE-A3 and MAGE-A6 genes combined it is 37% to 41%, and in patients with relapsed multiple myeloma, the positive expression rate for the MAGE-A3 and MAGE-A6 genes significantly increases to 77%, for the MAGE-A12 gene it is 20%. The positive expression rate for the MAGE-C1 gene is 77%, and for the MAGE-C2 gene it is 50% to 59%. High expression of MAGE-C1 may be associated with an increased plasma cell proliferation index, reflecting the activity and aggressiveness of the disease. Additionally, in non-transplant patients, the expression of MAGE-C1 is an independent prognostic factor [82, 83].

For liver cancer patients, high expression levels of the genes MAGE-A6 and MAGE-A12 are significantly correlated with the prognosis of HCC patients, suggesting they may be associated with the severity and progression of the disease. In contrast, low expression levels of the genes MAGE-A10, MAGE-B4, and MAGE-C3 are associated with a better prognosis in HCC patients [84].

Additionally, a comprehensive survival analysis of MAGE-I family members across various cancer types was conducted (Figure 7), with data provided on the Kaplan-Merier plotter website (https://kmplot.com/analysis/). To facilitate a direct comparison of hazard ratios, those with a $P \leq 0.05$ were selected and graphically represented, indicating a statistically significant association with patient survival outcomes (non-significant results, i.e., $P > 0.05$, are depicted in gray). The analysis revealed that in colorectal adenocarcinoma (COAD), gastric cancer, lung adenocarcinoma, and myeloma, the HR values of most MAGE genes are greater than 1, indicating that their upregulated expression is associated with poorer survival outcomes (a reduced likelihood of long-term survival). In contrast, in BRCA and OV, the HR values are less than 1, suggesting that their upregulated expression is inversely associated with poor survival outcomes (indicating a potential protective effect on long-term survival).

The MAGE family as targets for cancer immunotherapy: clinical progress, efficacy, safety evaluation, and challenges

Clinical and preclinical trials of immunotherapy against MAGE family proteins have focused on the MAGE-A of the MAGE-I family to evaluate its safety and efficacy. Under normal conditions, the expression of MAGE-A in somatic cells is tightly regulated, predominantly occurring in tissues such as the testis, which are typically non-responsive to immune responses. However, in a variety of cancer types, the expression of MAGE-A is reactivated and is associated with cancer progression, metastasis, and therapeutic resistance, exhibiting cancer specificity. This characteristic makes MAGE-A an ideal target for cancer-specific therapy, as its expression in cancer cells can be specifically targeted without harming normal cells. Below are some advancements in clinical and preclinical trials for therapies targeting MAGE-A in the treatment of various cancers (Table 4).

Table 4 MAGE-A related preclinical and clinical trials

ClinicalTrials.gov ID	Status	Cancer type	MAGEA family genes	Phase	Study year	Number of patients	HLA type	Treatment	Reference
Preclinical trial	–	Melanoma cell	MAGE-A1	–	–	–	–	–	[85]
		Melanoma mice model	MAGE-A1, A2, A3, A5, A6, and A8						[86]
		NOG mice with oesophageal and lung cancer cell lines	MAGE-A4						[87]
NCT02410733	Completed	Melanoma	MAGE-A3 and NY-ESO1	I	2015–2023	119	–	Lipo-MERIT	[88]
NCT00086866	Not provided	Melanoma	MAGE-A3	II	2004–2007	165	–	D1/3-MAGE-3-His fusion protein	[89]
NCT01435356	Terminated	Bladder cancer	MAGE-A3 and AS-15	II	2011–2017	83	–	recMAGE-A3 + AS15 ASCI	[90]
NCT01273181	Terminated	Melanoma, synovial sarcoma, and oesophageal cancer	MAGE-A3	I, II	2010–2012	9	HLA-A 2	PG13-MAGE-A3 TCR9W11 (anti-MAGE-A3/12 TCR) Transduced autologous peripheral blood lymphocytes	[91]
UMIN000003489[a]	Completed	Colon cancer	MAGE-A4	I	2009–2012	–	–	MAGE-A4- or Survivin-hepler pepitde (1 mg) vaccine, mixed with montanide and OK432 (picibanil; 0.2 KE)	[92]
NCT03132922	Active, not recruiting	Synovial sarcoma, ovarian cancer, head and neck cancer, and oesophageal cancer	MAGE-A4	I	2017–2022	71	HLA-A 2	Autologous genetically modified MAGE-A4^{c1032} T cells combined with low dose radiation	[93]
NCT02989064	Completed	Head and neck squamous carcinoma, melanoma, and urothelial carcinoma	MAGE-A10	I	2010–2020	10	HLA-A 2	Autologous genetically modified MAGE A10^{c796} T cells	[94]
NCT01241162	Completed	Neuroblastoma and sarcoma	MAGE-A1, MAGE-A3, and NY-ESO-1	I	2010–2016	19	–	Autologous dendritic cell vaccine with adjuvant	[95]

In melanoma cells, the specific recognition of MAGE-A1/HLA-A1 by chimeric receptors based on the Fab fragment resulted in the induction of TNF-α and IFN-γ, leading to the lysis of melanoma cells [85]. For patients with stage II melanoma treated with recombinant MAGE-A3 protein, the results showed complete remission in three patients, and all patients developed humoral and cellular immune responses against MAGE-A3, demonstrating good tolerability [89]. In a phase I clinical trial, an RNA liposome vaccine encoding MAGE-A3 and NY-ESO1 was used. The results showed that the vaccine was able to induce the production of IFNα and a strong antigen-specific T-cell response, with one patient achieving complete remission [88]. A Phase II clinical trial was conducted using a vaccine adjuvanted with MAGE-A3 in combination with AS-15 on patients with muscle-invasive bladder cancer post-cystectomy to evaluate its safety and efficacy. The results showed that compared to the placebo, the experimental group experienced some adverse reactions [90]. In addition, clinical trials have been reported for MAGE-A3: nine patients with melanoma, synovial sarcoma, and esophageal cancer were treated with autologous anti-MAGE-A3 T-cell receptor (TCR) engineered cell therapy in combination with chemotherapy. Results showed that two patients were in sustained remission 12 months after treatment, however, two patients had adverse events that led to study discontinuation [91].

In a phase I clinical trial, a helper/killer hybrid epitope long-peptide vaccine targeting MAGE-A4 was used in patients with colorectal cancer. The results showed that the vaccine was able to induce $CD4^+$

and $CD8^+$ T-cell responses, as well as MAGE-A4-specific IgG antibodies [92]. Adoptive T-cell transfer and peptide vaccination targeting MAGE-A4-expressing esophageal and lung cancer cell lines in NOG mice resulted in effector T-cell multifunctionality, indicating the anti-tumor efficacy of cytotoxic T lymphocytes [87]. What's more, an autologous T cell therapy targeting MAGE-A4 positive solid tumors—Afamitresgene autoleucel was investigated. It uses a lentiviral vector to transduce T cells expressing high affinity and specificity for a particular peptide segment of MAGE-A4. The therapy was assessed for safety and efficacy in patients with relapsed/refractory metastatic solid tumors such as synovial sarcoma, ovarian cancer, head and neck cancer, and esophageal cancer. The results showed an overall PR rate of 24% (9/38) among the patients. Specifically, the response rate for synovial sarcoma SS patients was 44% (7/16), while the response rate for patients with other cancer types was 9% (2/22). Besides, patients experienced toxicity during the trial [93].

Gene-engineered autologous T cells targeting MAGE-A10 were administered to four patients with advanced HNSC expressing MAGE-A10, three patients with melanoma, and three patients with urothelial carcinoma. The results showed disease stabilization in four patients, with no evidence of treatment-related toxicity [94].

In addition to therapies that target the MAGE-A family alone, there are also studies targeting multiple family proteins. For example, a consensus sequence DNA vaccine for multiple members of the MAGE-A family (MAGE-A1, A2, A3, A5, A6, and A8) was studied in a melanoma mouse model. The results showed that the vaccine could elicit a robust immune response, slow tumor growth, and extend survival [86]. In a phase I clinical trial, a dendritic cell vaccine targeting MAGE-A1, MAGE-A3, and NY-ESO-1 along with decitabine was used in patients with neuroblastoma and sarcoma, with one patient achieving complete remission and 5 out of 10 patients experiencing decitabine-related myelosuppression [95].

Despite early clinical trials demonstrating that immunotherapies targeting members of the MAGE-A family can induce humoral and cellular immune responses against tumors, including DNA/RNA vaccines, T cell autologous therapy, and combination treatments with chemotherapy drugs, achieving complete remission in some patients, they show great potential as targets for immunotherapy. However, their clinical application still faces some challenges, low expression of MAGE-A antigens in normal tissues may trigger an autoimmune response, leading to treatment-related toxicities such as rashes, diarrhea, and hepatitis. MAGE-A family proteins are mainly expressed in cytoplasm or nucleus and need to be presented to $CD8^+$ T cells through MHC (Major histocompatibility complex) class I molecules to activate cytotoxic T cell response. However, tumors may evade recognition and attack by the immune system by down-regulating the expression of MHC-I molecules, which limits the effectiveness of MAGE-A targeted immunotherapy. In addition, when using MAGE-A to target TCR or CAR T cell therapy, unexpected toxicity may result due to the cross-reactivity of TCR. In conclusion, although MAGE-A antigens have shown potential in clinical trials, immunotherapy strategies for intracellular antigens are still in the research and development phase, and more clinical data are needed to verify their safety and efficacy.

For members of the MAGE-II family, there are only relevant studies on MAGE-D4. For the first time, researchers have identified a specific antigenic peptide of MAGE-D4 in kidney cancer samples, which can bind to HLA-A*25 molecules [96]. In addition, studies have also confirmed that the use of MAGE-D4 antigen peptide successfully induced an immune response against tumors in vitro experiments [97].

In general, the MAGE family, especially MAGE-A, have emerged as potential targets for cancer immunotherapy, showing the capacity to stimulate immune responses and achieve remissions in early clinical trials. Despite this, challenges such as autoimmunity risks and tumor evasion strategies limit their widespread application. Future research is crucial to refine these therapies for improved safety and effectiveness.

Conclusion

The aberrant expression of MAGE family genes across various cancers and their multifaceted roles in tumor biology have positioned them as significant targets in cancer research and therapy. The MAGE family includes MAGE-I and MAGE-II family. MAGE-I family members not only exhibit abnormal activation in a multitude of tumors but also show a close correlation between their expression patterns and the clinical characteristics and prognosis of the tumors. The involvement of MAGE-I family genes in regulating several critical processes of tumor cells, such as proliferation, apoptosis, immune evasion, DNA damage repair, and metastasis, has provided new molecular markers and potential therapeutic targets for the early diagnosis, treatment, and prognostic assessment of cancer. However, the mechanisms by which MAGE-I family genes operate in cancer are not yet fully understood, necessitating further research to elucidate their detailed molecular mechanisms and to determine how to safely and effectively leverage these targets for treatment.

Among many MAGE genes, the MAGE-A family was the most intensively studied and has shown greater potential in preclinical and clinical trials as targets for cancer immunotherapy. Despite the MAGE-A family proteins are mainly expressed in the cytoplasm and nucleus, which poses a challenge for tumor immunotherapy, these research outcomes have still provided valuable information and experience for cancer immunotherapy. Additionally, the MAGE-II family, including MAGE-D, MAGE-E, MAGE-F, MAGE-G, MAGE-H, MAGE-L, and Neddin, were less studied, and their expression patterns require further validation through large-sample studies. The identification and confirmation of regulatory factors for MAGE-II genes are also areas that necessitate more research and deeper understanding of the biological characteristics and molecular mechanisms of MAGE-II genes will be crucial. Looking ahead, with an in-depth understanding of the functions of MAGE family genes and the development of novel immunotherapeutic strategies, the MAGE family is expected to become a significant breakthrough in the field of cancer treatment.

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