

Regulation of Transcription Factors by Tumor-Specific MAGE Proteins

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ABSTRACT

The tumor specific melanoma antigen gene (MAGE-I) family was initially considered promising and selective targets for immunotherapy. Currently, their functional characterization points to a role in transcription regulation. In this article we focus on MAGE-A proteins as regulators of transcription factors involved in different cancer-related pathways and how this regulation could contribute to tumorigenesis.

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Key words: MAGE; Transcription Factors; Cancer Disease

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INTRODUCTION

Melanoma Antigen Genes (MAGE) constitutes a multigenic family divided in two subfamilies, MAGE-I and MAGE-II, according to its tissue pattern expression. While MAGE-I in adult humans are only expressed in testis and tumors tissues, those belonging to MAGE-II subfamily are ubiquitously expressed.

The first members of MAGE family were discovered in 1991, when van der Bruggen *et al*^[1] performed a screening aimed to identify tumor specific antigens from MZ-2 human melanoma cell line. Since then, the MAGE family has been growing and nowadays it includes more than 50 proteins containing a highly conserved module of approximately 200 amino acids, denominated Mage Homology Domain (MHD).

All MAGE-I genes are clustered in three different regions of the X chromosome, forming the MAGE-A, MAGE-B and MAGE-C groups, which belong to the group of Cancer Testis Antigens (CTAs). On the other hand, MAGE-II loci are not restricted to the X chromosome.

At the beginning, the tumor-specific pattern expression of MAGE-I proteins was used as diagnostic markers to identify almost undetectable tumor mass^[2-4]. Besides, MAGE-I proteins are potentially useful as prognosis markers. However, due to MAGE-I highly conserved homology their function was a priori considered redundant, delaying the understanding of the roles that MAGE proteins performed in tumor cells. Fortunately, during the last decade, several functional characterizations of MAGE-I proteins were performed and currently growing evidence points to a role of MAGE-I proteins, especially MAGE-A proteins, in the regulation of transcription through the regulation of specific transcription factors.

In this article we focus on MAGE-A proteins as regulators of transcription factors involved in different cancer-related pathways and how this regulation could facilitate tumor development or its response to treatments. Data presented here support the idea that

MAGE proteins could actively play a central role in development and progression of cancer disease.

MAGE-A1 REPRESSED TRANSCRIPTION BY INTERACTING WITH SKIP AND HDAC1

In order to shed light on MAGE-A functions, Laduron *et al.*^[5] performed a yeast-two-hybrid screen to identify MAGE-A1 interacting proteins. As a result, SKIP, an adaptor protein involved in transcriptional regulation, was identified as a MAGE-A1-associated protein. This interaction was also confirmed in mammalian cells.

Functional assays showed MAGE-A1 inhibits the SKIP-dependent transcriptional activity of Notch1 pathway. In this pathway, ligand binding to the Notch1 receptor releases Notch1-IC, which enters the nucleus and regulates gene expression. In the absence of Notch1-IC, C-promoter binding factor 1 (CBF1) inhibits transcription by binding SKIP and a co-repressor complex. When Notch1-IC enters the nucleus, it binds to SKIP and CBF1, displaces the repression complex and recruits co-activators. Focused on this pathway, Laduron *et al.*^[5] showed MAGE-A1 was able to counteract the transcriptional activation mediated by Notch1-IC and proposed different possibilities: i) MAGE-A1 displaces Notch1-IC from SKIP, or ii) MAGE-A1 leaves Notch1-IC attached to SKIP but masks Notch1-IC sites involved in transcriptional activators recruitment, or iii) MAGE-A1 functions as an active repressor after binding to SKIP. In this respect, MAGE-A1 was co-immunoprecipitated with transcriptional repressor HDAC1 and a cooperative repression was observed when both proteins were co-expressed.

Notch1 mediates intercellular communications and directs cell fate decisions during development, so, it is possible that MAGE-A1 participates in cell fate choices during spermatogenesis. However, as SKIP is involved in several signaling pathways, repression by MAGE-A1 bound to SKIP may have broader biological effects.

In addition, MAGE-A1 is expressed in tumor cells, which usually have altered HDAC activities. Therefore, by recruiting HDAC1 to promoters that remain to be identified, MAGE-A1 may contribute to transcription alterations to favor tumor cell growth.

Overall, by binding to SKIP and also by recruiting HDACs, MAGE-A1 can act as a potent transcriptional repressor of this pathway.

MAGE-A2 REPRESSES p53 TRANSCRIPTIONAL ACTIVITY

The regulation of p53 transcriptional activity by MAGE-A2 was first reported by our group in 2006^[6] and currently it is one of the best characterized activities for a MAGE-A protein.

Several mechanisms have been proposed to explain how MAGE-A2 inhibits p53 transcriptional activity. By performing biochemical and cellular assays, we proposed a mechanism involving the recruitment of histone deacetylases (HDACs), with the consequent hypoacetylation of activated p53 and the histones surrounding p53-binding sites.

We evidenced that MAGE-A2-HDAC3 is a p53-repressing complex, where MAGE-A2 acts as a p53-HDAC3 complex assembling protein. We also observed a direct interaction between MAGE-A2 and p53-DNA-binding domain. Moreover, we observed a correlation between MAGE-A expression levels and resistance to apoptosis induced by DNA-damaging agents in short-term cell lines obtained from melanoma biopsies harboring wild-type p53. In addition, combined treatment with HDACs inhibitors and

chemotherapeutic drugs restored the p53 response and reverted chemoresistance^[6].

Later, Doyle *et al.*^[7] identified RING domain proteins NSE1, LNX1, PRAJA-1 and the previously reported KAP1^[8] as binding partners of MAGE proteins and also observed that MAGE expression enhances the E3 ubiquitin-ligase activity of these RING domain-containing proteins. Of special interest, MAGE-A2 and MAGE-C2 enhance “*in vitro*” the E3 ubiquitin ligase activity of KAP1 using p53 as substrate. As a consequence, a proteasome-dependent reduction of p53 protein level was observed in cells expressing MAGE-A2 or MAGE-C2^[8].

Recently, Marcar *et al.*^[9] reported a mechanism to explain how MAGE-A proteins represses basal p53 transcriptional activity in the absence of external insults: they found that MAGE-A2 interacts with the DNA binding surface of the p53 core and, in the absence of p53 stimulation, MAGE-A silencing leads to increased recruitment of p53 to p21, MDM2 and PUMA promoters with their consequent induction at mRNA and protein levels. Based on this data, the authors suggest that MAGE-A proteins block the association of p53 with its cognate sites within chromatin, thus interfering with basal p53 transcriptional activity^[9]. Interestingly, these results suggest a mechanism whereby MAGE-A proteins could inactivate basal transcriptional activity of p53 in the absence of stress, a highly relevant topic for its tumor suppressor function^[10-12]. Probably, after stabilization and activation of p53 through DNA damaging agents, this mechanism could be switched and reinforced through the recruitment of transcriptional repressors, namely HDACs or KAP1.

The promyelocytic leukemia (PML) tumor suppressor protein, responsible for PML Nuclear Bodies (PML NBs) formation, is a regulator of p53 acetylation and function during cellular senescence. Senescence triggering is a tumor-suppressive mechanism which constitutes a critical barrier against cellular transformation^[13]. Recently, we observed that MAGE-A2 efficiently binds to PMLIV and affects its acetylation and sumoylation, required for PML-NBs formation and p53 activation. Consequently, MAGE-A2 expression impairs oncogene activated senescence in normal cells. RasV12 expression in human diploid fibroblasts induces senescence to counteract oncogene-induced growth signals. When RasV12 is activated, cells expressing MAGE-A2 skip senescence and grow, suggesting that MAGE-A2 could favor oncogene driven cell transformation by targeting PML/p53 axis^[13]. Besides, this demonstrates that MAGE-A proteins could have an impact on other p53 functions different from apoptosis, highlighting their relevance in cancer development.

The above described mechanisms about how MAGE-A2 regulates p53 activity are different but not necessarily incompatible and could depend on: (i) the level of p53 activation (i.e. steady state levels versus activation by DNA-damage, PMLIV or oncogene expression); (ii) the cellular context (cell type and relevant MAGE-I members expressed) and (iii) the availability/expression of MAGE-I partners (HDACs, RING proteins)^[14].

MAGE-A3 REGULATES KRAB ZINC FINGER TRANSCRIPTION FACTORS

In 2007, Yang and co-workers reported that MAGE proteins can act as co-repressors of p53 by binding to KAP1 and enhancing its suppression of p53^[8].

KAP1 is a co-repressor and ubiquitin E3 ligase required by the Kruppel-associated box (KRAB) domain containing zinc fingers transcription factors (KZNF). These transcription factors function

by directing the KAP1 complex to specific genes, causing chromatin condensation and therefore transcriptional repression^[15].

By using recombinant proteins containing different KRAB domains fused to the GAL4-DNA binding domain (GAL4-DBD) and a cell line containing an integrated KRAB-DBD responsive reporter gene, Xiao *et al* showed MAGE-A3 can differentially modulate KZNFs depending on their KRAB domain^[15]. Of special interest, MAGE-A3 is able to release transcriptional repression caused by ZNF382, a KZNF that has been shown to be a tumor suppressor^[16]. Similar results were previously observed with MAGE-C2, suggesting MAGE-I proteins could act as regulators of master transcription factors affecting cascades of gene activity.

MAGE-A4 BINDS TO MIZ-1 AND INDUCES APOPTOSIS

MAGE-A4 interacts with Gankirin, an oncoprotein overexpressed in Hepatocellular carcinoma (HCC), and suppresses its tumorigenic activity^[17]. It has been demonstrated that the C-terminal 107 amino acids of MAGE-A4 were able to induce both p53-dependent and independent apoptosis^[18]. It was shown that this fragment of MAGE-A4 increased p53 protein levels but decreased p21 transcript and protein levels. By performing a yeast-two-hybrid assay, it was found that C-terminal of MAGE-A4 interacts with the POZ domain/zinc finger transcription factor Miz-1. This interaction was also observed in mammalian cells. Miz-1 transcription factor binds to the proximal promoter region of the p21 gene, and together with p53 enhances its transcription^[19]. The C-terminal region of MAGE-A4 is recruited to the p21 promoter through its interaction with Miz-1. Although binding of C-terminal MAGE-A4 does not affect the association of Miz-1 to p21 promoter, it inhibits the trans-activating activity of Miz-1 on p21, resulting in the induction of apoptosis^[18].

Opposite to other reported function for MAGE-A proteins, C-terminal MAGE-A4 seems to have anti-tumor and pro-apoptotic activities. A complete understanding of MAGE-A4 functions would allow the use of C-terminal MAGE-A4 as a therapeutic tool against cancer disease.

MAGE-A11 REGULATES TRANSCRIPTIONS FACTORS INVOLVED IN DIFFERENT CELLULAR PATHWAYS

Among MAGE-A proteins, MAGE-A11 is the only one currently reported to regulate several transcription factors, belonging to different cellular pathways.

MAGE-A11 is a co-regulator of Steroid Receptors

MAGE-A11 regulates Androgen Receptor

Androgen Receptor (AR) is a ligand dependent transcriptional factor which has a critical role in sexual development as well as tumor formation and progression of prostate cancer^[20].

AR structure includes the Activation Function 2 motif (AF2) in its Ligand Binding Domain (LBD), capable of binding LXXLL motifs of steroid receptor co-activators but with preference to the FXXLF motif (23FQNLF27) present in the AR N-terminus itself^[21,22]. Binding of testosterone or dihydrotestosterone (DHT) induces the AR amino- and carboxyl-terminal (N/C) interaction between the AR dimmers and induces gene transcription of its target genes.

Contrary to transcriptional repression roles reported for most of

MAGE proteins, MAGE-A11 is an AR transcriptional co-activator. Also, MAGE-A11 expression levels correlates with AR enhanced activation in prostate cancer cells^[23].

MAGE-A11 dimmers are capable of binding to AR FXXLF motif through its F-box, a highly conserved repeating sequence of hydrophobic amino acids located between residues 329-369, within MAGE-A11 MHD. This interaction is modulated by mitogen activated protein (MAP) kinase that mediates MAGE-A11 phosphorylation in Ser174 in response to serum stimulation. MAGE-A11/AR binding competes with the AR N/C interaction and enhances AR dimmers transcriptional activity by increasing accessibility of AF2 for the recruitment of co-activators such as p300 and TIF2^[23]. In addition, MAGE-A11 is also able to interact and recruit p300 and TIF2 through its MXXIF (185-MDAIF-189) and FXXIF (260-FPEIF-264) motifs, respectively^[24,25]. Interestingly, the TIF2 interacting motif is conserved in most of MAGE-A members and some MAGE-B members, however, the p300 interacting motif is a unique feature of MAGE-A11, suggesting that MAGE-A11 is an important AR co-regulator increasing AR transcriptional activity during prostate cancer progression^[26].

Latter, posttranslational modifications in MAGE-A11 with consequences in AR/MAGE-A11 complex and increased AR activity, were reported^[27]. The Epidermal Growth Factor (EGF) induces Chk1 kinase mediated phosphorylation of Thr360 and monoubiquitination in Lys240 and 245 within the MHD of MAGE-A11, the same residues required for the MAGE-A11/AR interaction. Both phosphorylation and monoubiquitination stabilize MAGE-A11, while polyubiquitination marks it for proteasome-dependent degradation. EGF promotes the formation of a stable complex between AR-DHT-MAGE-A11 and therefore increased AR transcriptional activity and a more rapid turnover of both AR and MAGE-A11.

Besides the precise information we have about the interaction between MAGE-A11, AR and its co-regulators, the biological consequence of MAGE-A11 expression is the amplification of AR signaling and promotion of tumor growth in a low circulating androgen environment.

MAGE-A11 specifically regulates Progesterone Receptor-B

Progesterone regulates the uterine myometrium in pregnancy by maintaining the quiescence of the myometrial cells in an anti-proliferative manner. Besides its aberrant expression in cancer cells, MAGE-A11 is also expressed at low levels in human reproductive tracts of male and female and during the menstrual cycle^[28].

It was reported that MAGE-A11 can also regulate human Progesterone Receptor-B (PR-B)^[29]. The specific NH2-terminal 110-LLXXVLXXLL-119 motif in PR-B interacts with the MAGE-A11 F-box region in a phosphorylation and ubiquitylation-dependent manner. This NH2-terminal region is involved in PR-B down-regulation induced by progesterone and is required for the co-regulatory effects of MAGE-A11 and p300 on PR-B^[29].

MAGE-A11 region required for PR-B and AR interaction is the same, and in both cases MAGE-A11 works synergistically with p300 and p160 co-activators to increase the transcriptional activity of AR and PR-B. However, this interactions result in different biological effects, as a down-regulation of PR-B in the absence of progesterone and the stabilization of AR in the absence of androgen^[23]. But in the presence of progesterone, the PR-B/ MAGE-A11 interaction enhances PR-B specific progesterone-dependent gene activation, as reported for the immunophilin FKBP5.

The transcriptional enhancing effects of MAGE-A11 on progesterone-dependent gene expression expands the role of

MAGE-A11 in steroid hormone signaling, in this case by maximizing transcriptional response in normal human physiology.

MAGE-A11 activates hypoxic response through stabilization of HIF1- α

As the tumor mass increases, the amount of oxygen and glucose required for tumor growth becomes limited. Tumors adapt to this condition through stabilization of hypoxia-inducible factors (HIFs) which activate transcription of pro-angiogenic proteins^[30].

MAGE-A11 was shown to regulate hypoxic response through inhibition of the Hypoxia-inducible factor Prolyl Hydroxylase 2 (PHD2)^[31]. Under normal oxygen conditions, PHD2 hydroxylates the HIF α subunit of HIF, allowing its degradation by the E3-ubiquitin ligase pVHL. When oxygen is limited, the HIF- α subunits are stabilized, translocate into the nucleus where heterodimerized with HIF- β and activate their target genes.

It was demonstrated that MAGE-A11 interaction with PHD2 does not change PHD2 protein levels but rather suppress its activity. In line with this, down-regulation of MAGE-A11 by siRNA results in impaired HIF1- α induction by hypoxia and inhibition of hypoxia-induced transcription of HIF target genes.

The capability of MAGE-A11 to modulate stability of HIF- α could enhance cellular responses to hypoxia and favor tumor mass development.

MAGE-A11 modulates E2F1 activity through interaction with p107 pocket protein

The retinoblastoma family members: pRB, p107 and p130 are involved in cell cycle regulation through the modulation of E2F transcription factors. It has been recently reported that MAGE-A11 is able to interact with members of the pocket protein family as p107 and, to a lesser extent, pRB^[32].

Interaction of MAGE-A11 with p107 results in p107 stabilization by inhibition of ubiquitination. MAGE-A11 is also able to interact with endogenous hypophosphorylated form of E2F1 and cause an increased in E2F1 transcriptional activity.

MAGE-A11-dependent increased in E2F1 transcriptional activity is similar to that observed with the viral oncogene E1A (human adenoviral early region protein E1A) which is able to transform cells by activating E2F1 through competitive interaction with proteins from the Rb family.

By assessing the effects of several mutants of MAGE-A11 in the activation of E2F1, it has been suggested that MAGE-A11/p107 interaction releases transcriptional active E2Fs, similar to adenovirus E1A. Authors also observed E2F1 strongly associates with p107 in prostate cancer cell with endogenous expression of MAGE-A11, and proposed MAGE-A11 expression in prostate cancer cells could reverse p107 from a transcriptional repressor to a transcriptional activator of E2F1.

Table 1: Transcription factors regulated by MAGE proteins.

MAGE Protein	Transcription Factor Reg-ulated	Process Affect-ed	Cite
MAGE-A1	Notch1-IC	Spermatogenesis	[5]
MAGE-A2	p53	Apoptosis	[6-9]
	PML	Senescence	[13]
MAGE-A3	KZNF	Transcriptional repression	[15]
MAGE-A4	Miz-1	Apoptosis	[18]
MAGE-A11	AR	Cell proliferation	[21-27]
	PR-B	Reproduction	[29]
	HIF- α	Hypoxia	[31]
	E2F1	Cell proliferation	[32]

These results, in addition to those described above, suggest a positive regulation of AR, HIF- α and E2F1 transcription factors by MAGE-A11 that overall contribute to its oncogenic potential.

CONCLUSION

Data revised here show a common feature of some proteins belonging to MAGE-A group: their capacity to regulate transcription and transcription factors involved in cellular pathways related to cancer. This property could be a general mechanism by which MAGE proteins could drive tumorigenesis. Therefore, the precise understanding of this regulation and its biological consequences will undoubtedly facilitate the development of therapeutic approaches against cancer.

CONFLICTS OF INTEREST

The Authors have no conflicts of interest to declare.

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