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Mini-review

# Tumor-specific MAGE proteins as regulators of p53 function

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ABSTRACT

Since its discovery in 1991, the knowledge about the tumor specific melanoma antigen gene (MAGE-I) family has been continuously increasing. Initially, MAGE-I proteins were considered as selective targets for immunotherapy. More recently, emerging data obtained from different cellular mechanisms controlled by MAGE-I proteins suggest a key role in the regulation of important pathways linked to cell proliferation. This is in part due to the ability of some MAGE-I proteins to control the p53 tumor suppressor. In this review, we focus on the mechanisms proposed to explain how MAGE-I proteins affect p53 functions.



## 1. Overview of MAGE family: discovery, organization and expression

The first members of Melanoma Antigens Genes (MAGE) family were discovered in 1991, when van der Bruggen et al. performed a screening to identify tumor specific antigens from melanoma cells [1]. In this landmark work, the "MAGE iceberg tip" was identified: MAGE-1 together with two closely related proteins, MAGE-2 and MAGE-3 (now, MAGE-A1, -A2 and -A3). Since then the MAGE family has been growing and nowadays it includes more than 50 proteins containing a *Mage Homology Domain* (MHD), a highly conserved module of approximately 200 amino acids.

Based on its tissue pattern expression, MAGE family is divided into two subfamilies: MAGE-I and MAGE-II. MAGE-I are tumor-specific proteins belonging to the group of Cancer Testis Antigens (CTAs), since their expression is restricted to cancer cells and testis. All MAGE-I genes are clustered in three different regions of the X chromosome, forming the *MAGE-A*, *MAGE-B* and *MAGE-C* groups. Conversely, proteins belonging to MAGE-II subfamily are ubiquitously expressed; posses a less conserved MHD and their loci are not restricted to the X chromosome. Among them, NECDIN and members of MAGE-D and MAGE-G groups are representative proteins of the MAGE-II subfamily. Although very little is currently known about most of these genes, their respective proteins were reported to be involved in cell cycle regulation, apoptosis and neurogenetic diseases [2].

MAGE-I transcriptional expression is mainly regulated by epigenetic events. Whereas in untransformed cells MAGE-I genes are silenced by DNA methylation, epigenetic reprogramming in tumor cells leading to global DNA hypomethylation correlates with expression of a variety of *MAGE-I* and other *CTAs* genes [3,4]. Moreover, *MAGE-I* genes are highly sensitive to histone and DNA methylation status. In fact, disruption of *G9a* or *Glp* histone methyl transferase genes in mouse embryonic stem cells correlates with MAGE-A mRNAs expression [5,6]. Also, HCT116 human colon cancer cells knock-out for the DNA methyl transferases *DNMT1* and *DNMT3b*, strongly reduce *MAGE-A1* promoter methylation [7]. In addition, it was reported that both the CTA BORIS (Brother of the

*Abbreviations:* MAGE, melanoma antigen gen; MHD, MAGE homology domain; CTAs, cancer testis antigens; Glp, G9a-like protein; HCT116, human colon cancer cell line-116; DNMT1/3b, DNA (cytosine-5)-methyltransferase 1/3 beta; BORIS, brother of the regulator of imprinted sites; c-KIT, cellular Tyrosine protein kinase; DBA2 mice model, dilute brown non-agouti mice model; HDACs, histone deacetylases; TSA, trichostatin A; KAP1, KRAB-ZFP-associated protein 1; MDM2, murine double minute 2; RING, really interesting new gene; LNX1, ligand of numb-protein X 1; TRIM28, tripartite motif-containing 28; PUMA, p53 upregulated modulator of apoptosis; PML-NBs, promyelocytic leukemia-nuclear bodies; MM, multiple myeloma; NRAGE, neurotrophin receptor-interacting MAGE homolog; BRCA-2, breast cancer type 2 susceptibility protein; p75NTR, p75 neurotrophin receptor; AR, androgen receptor; AF2, activated function 2; CTCF, CCCTC-binding factor; 3'UTR, 3′ untranslated region.

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regulator of imprinted sites) and the oncogene c-KIT can induce MAGE-I expression by regulating methylation of their promoters [8,9]. Interestingly, in vivo studies performed in mice have shown that genome hypomethylation promotes tumor formation [10], lending support to the view that MAGE-I expression could collaborate with cancer development.

The tumor-specific pattern expression of MAGE-I proteins make them extremely attractive for the oncology field. Such expression specificity allows the use of MAGE-I proteins as diagnostic indicators, to identify usually undetectable tumor mass [11–13]. Besides, MAGE-I proteins are potentially useful as prognosis markers. Indeed, since their discovery, a number of different reagents for MAGE-I detection in human tumor samples have been developed and, in the last years, the performance of studies correlating MAGE-I tumor expression and clinical stages of disease have significantly increased [14].

The relationship between MAGE expression and tumor growth has also been supported by gene manipulation in animal models. Compelling results indicate that MAGE-I proteins are involved in tumorigenesis, resistance to chemotherapeutic agents, aggressiveness and cancer disease progression [15,16]. It has been reported that regulation of MAGE expression by MAGE-specific small interfering RNA reduced mast cells and melanoma tumor growth in a syngeneic DBA2 mice model [9,15]. Moreover, forced expression of MAGE-A3 promotes thyroid carcinoma tumor growth, cell migration, invasion and lung metastasis in an orthotopic mice model [16].

In addition to the study of MAGE-I proteins as tumor markers, they have also been tested as promising targets for immunotherapy [17]. Even though, there is still limited information about MAGE-I protein function in tumor cells, contributions to this field have been recently made. However, further research is necessary to thoroughly understand MAGE-I involvement in the development and/or maintenance of cancer.

In this article we review the relationship between MAGE-I proteins and the tumor suppressor p53. We discuss the mechanisms proposed to explain how MAGE-I proteins affect p53 anti tumor activity and how this knowledge could help to improve new therapies against cancer disease.

## 2. MAGE-I expression and p53 transcriptional response

p53 is a highly sensitive transcription factor activated by a variety of damaging or stressful signals that compromise normal cellular behavior. DNA damage and oncogene expression are key stimuli for p53 activation [18,19]. It involves p53 post-translational modifications and its accumulation into the nucleus. Once there, p53 recognizes a consensus sequence on its target promoters and activates a selective gene expression program. p53 target genes are mainly involved in cell cycle-controlling pathways such as apoptosis, cell growth arrest and senescence [20]. For this reason, the p53 pathway is critical to controlling oncogenesis. More than 50% of human cancers harbor inactivating mutations on p53 [21]. Besides, wild-type p53 can also be inactivated by cellular proteins and oncogenic viral proteins [22]. Cells bearing non functional p53 are prone to undergo transformation and to form tumors hard to target by chemotherapeutic drugs, which strongly activate the p53-dependent apoptotic response.

Until recently, the function of MAGE-I proteins was completely unknown. Currently, growing evidence points to a role of MAGE-I proteins, especially MAGE-A proteins, in the regulation of transcription and some specific transcription factors. Works published by different research groups indicate that one of these transcription factors is the p53 tumor suppressor (Table 1). In the last years, different mechanisms have been proposed to explain how this regulation occurs.

**Table 1**
MAGE interacting proteins and their biological effects.

| MAGE protein | Interactor | Effect | References |
|---|---|---|---|
| MAGE-A1 | SKIP/ HDAC1 | Transcriptional repression through HDAC1 recruitment | [46] |
| MAGE-A2 | p53/ HDAC3 | Transcriptional repression of p53 through HDAC3 recruitment. Hypoacetylation of activated p53 and histones surrounding p53-binding sites | [23] |
| | p53 | Transcriptional repression through limiting the association of p53 to its binding sites within chromatin in unstressed cells | [28] |
| | PMLIV | Defects in PMLIV (TRIM19) acetylation, sumoylation and PML NBs formation. Hypoacetylation of p53 at PML NBs. Decreased senescence induced by oncogenes | [29] |
| MAGE[a] | KAP1 | Enhancement of KAP1 regulation p53-dependent apoptosis and protein levels Hypoacetylation of p53 | [15] |
| | RING proteins | Enhancement of E3 ubiquitin ligase activity of KAP1 (TRIM28), PRAJA-1 and LNX1 | |
| | | Regulation of p53 protein levels by MAGE-A2 and MAGE-C2 through KAP1 binding | [26] |
| | GANKYRIN | Suppression of anchorage-independent cell growth in vitro and tumor formation of GANKIRIN expressing cells in nude mice | [43] |
| MAGE-A4 | MIZ-1 | Transcriptional repression of *p21* promoter, induction of apoptosis and suppression of cell anchorage-independent growth in vitro and in vivo | [42] |
| MAGE-A11 | AR/TIF2/ p300 | Transcriptional activation of AR in prostate tumor cells | [47,48,51] |

The biological effects resulting from interactions between MAGE-A members and their interacting proteins are described. Interactions resulting in p53 regulation are highlighting in gray.
[a] The study includes different MAGE members.

In 2006 our group reported for the first time that MAGE-A2 protein was able to repress p53 transcriptional activity [23]. By performing biochemical and cellular assays, we proposed a mechanism involving the recruitment of transcriptional repressors, histone deacetylases (HDACs), and 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 the tumor antigen MAGE-A2 acts as a p53-HDAC3 assembling complex. We also observed a direct interaction between MAGE-A2 and p53, being p53-DNA-binding domain required for this interaction. 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 [23].

Subsequently, the involvement of MAGE-I proteins in the regulation of p53 and the apoptotic response was corroborated by other independent studies. In 2007, Yang et al. reported that KAP1 (also named TRIM28) associates to multiple MAGE-I proteins (including MAGE-A3, MAGE-C2 and a representative mouse Mage-b), and proposed a mechanism by which MAGE-I proteins act as co-repressors of p53 by binding to KAP1 [15]. Previously, it had been reported that KAP1/MDM2 complex regulates p53 activity and stability through enhancing the recruitment of HDAC1, thus

impairing p53 acetylation [24]. Similarly, KAP1 also represses E2F1 transcriptional activity through acetylation regulation and HDAC recruitment [25]. Yang and coworkers found that MAGE expression enhances the formation of KAP1/p53 protein complexes, promoting p53 de-acetylation as well as its transcriptional repression [15].

Later, in line with these results, Doyle et al. [26] identified different RING domain proteins as binding partners of MAGE proteins. Among them: NSE1, LNX1, PRAJA-1 and the previously reported KAP1. In most cases, MAGE proteins bind to one specific RING domain protein and similar MAGE proteins bind to the same RING protein, suggesting specificity in the interaction. The protein–protein interactions occur through the MHD, however, MAGE proteins do not recognize a common motif on their RING partners. Moreover, the RING domain is not required for the interaction. By performing biochemical assays, the authors observed that MAGE expression enhances the E3 ubiquitin-ligase activity of the RING domain-containing proteins. Of special interest, MAGE-A2 and MAGE-C2 enhance "in vitro" an E3 ubiquitin ligase activity of KAP1 using p53 as substrate, independently of MDM2. As a consequence, a proteosome-dependent reduction of p53 protein level was observed in cells expressing MAGE-A2 or MAGE-C2 [26]. Interestingly, it was also reported that KAP1's PHD domain can act as an E3 SUMO-Ligase for its own adjacent bromodomain [27]. The RING/MAGE mechanism proposed by Doyle et al. to ubiquitinate p53 seems to involve the recruitment of an E2 ubiquitin-conjugating enzyme to the MAGE/E3-Ligase complex to enhance the E3-Ligase activity of a specific TRIM protein. Recently, two models were suggested to explain how the E3 ubiquitin ligase activity of KAP1 could be activated through MAGE-C2 binding [28]. The first one supposes that binding of KAP1 and its E2 enzyme to MAGE-C2 are mutually exclusive. After transferring one ubiquitin to its substrate, the E2 molecule could be recharged by an E1 ubiquitin-activating enzyme, but in the proximity of the E3 machinery, due to its interaction with MAGE-C2. The second model proposes that MAGE-C2 could bind to KAP1 and the specific E2 enzyme at the same time. Thus, two E2 molecules would be recruited to the KAP1 machinery, one through the interaction with KAP1 domain and the other through the interaction with MAGE-C2. In this model, MAGE-C2 might promote the sequential assembly of a polyubiquitin chain on the substrate [28]. Whether MAGE-C2 could bind to KAP1 and E2 molecules at the same time is still an open question which has to be answered in order to validate these models.

Recently, Marcar et al. [29] reported an alternative mechanism to explain how MAGE-A proteins inhibit p53 transcriptional activity. Using a series of overlapping peptides encompassing the entire p53 sequence, they found that MAGE-A2 interacts with the DNA binding surface of the p53 core, a result which is in agreement with Monte et al. [23]. Marcar et al. reported that, 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 p53 transcriptional activity [29]. 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 [30–32]. 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.

More recently, we reported the involvement of MAGE-A proteins in cellular senescence, an important tumor-suppressive mechanism which constitutes a critical barrier against cellular transformation [33]. The promyelocytic leukemia (PML) tumor suppressor protein, responsible for PML Nuclear Bodies (PML NBs) formation, is a regulator of p53 acetylation and function in cellular senescence. We observed that MAGE-A2 (but not MAGE-A4) 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 [33]. 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-I proteins regulate 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). Probably, in unstressed cells, p53 is weakly bound to some of its specific promoters to keep basal levels of transcription. However, if tumor cells express MAGE-I proteins, a lower p53 activity could be attributable to an impaired p53 binding to DNA through MAGE-A2 interaction. In parallel, p53 protein levels could be reduced due to RING/MAGE interaction and the enhancement of proteosome-mediated degradation activity. However, under stress conditions, p53 protein accumulates, becomes acetylated, tetramerizes and tightly associates to DNA. In tumor cells expressing MAGE-A, p53 complex formation in the presence of the deacetylating machinery (HDACs and/or KAP1) results in a strong impairment in p53 function (Fig. 1).

The reported partners found in MAGE-A2 complexes include both HDACs (HDAC3) and TRIM proteins (KAP1/TRIM28 and PMLIV/TRIM19): it could be hypothesized that the end-point result of MAGE-A2 function is to foster the association of chromatin to HDAC-enriched sub-compartments where TRIM proteins could find their specific niche to impose their inhibitory effects. In this line of reasoning, down-regulation of KAP1 protein expression has been shown to result in a constitutive increase in PML NBs number, decreased nuclear lamina-associated heterochromatin and reduction in chromatin density, as reminiscence of DNA damaged chromatin [34]. In the same work it was shown that changes in chromatin ultrastructure also correlate with increased histone H4 acetylation, whereas treatment with the HDAC inhibitor TSA fails to further increase PML NBs number. Therefore KAP1-dependent changes in chromatin structure could regulate PML NBs number in response to DNA damage through ATM activation, since ATM phosphorylates and regulates KAP1 activity [35]. Probably, MAGE-A2 function could be associated to the organization of specific chromatin regions and nuclear-subdomains in tumor cells, through its interaction with KAP1 and the enhancement of KAP1 transcriptional repression function through direct recruitment of HDAC. In this way, it could prevent both sumoylation- and acetylation-dependent activities that regulate both PMLIV and p53 function on the chromatin contained within nuclear sub-domains (PML NBs).

In addition to the biochemical, molecular and cell biology approaches, a relationship between MAGE-I and p53 proteins was evidenced from samples belonging to patients with different kind of tumors. The analysis of human thyroid cancer samples (frequently harboring wild type p53) showed that tumors exhibited an increase in cytoplasmic MAGE expression in comparison to normal thyroid tissues. Besides, a positive correlation between cytoplasmic MAGE expression and histologically proven lymph node metastasis was observed. On the other hand, the authors reported

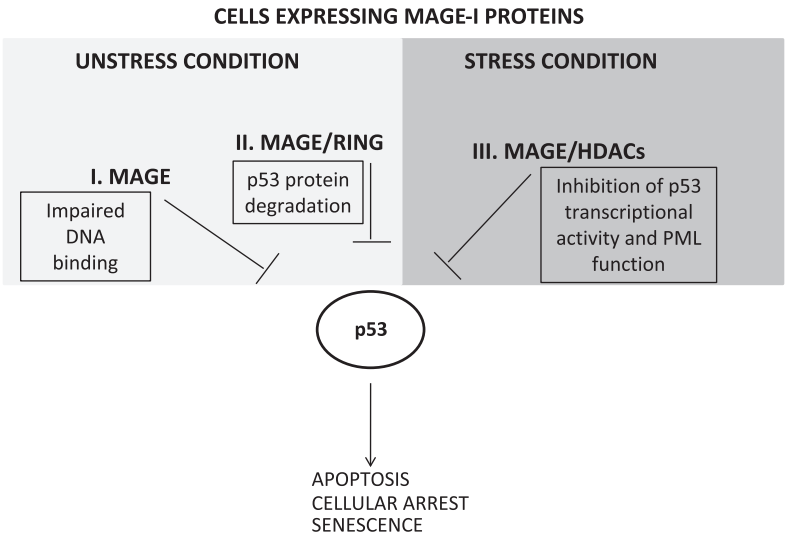


**Fig. 1.** Schematic representation of potential mechanisms used by MAGE-I proteins to regulate p53. (Left) In transformed and unstressed cells expressing MAGE-I, a low activity of p53 could be the consequence of its interaction with MAGE-I proteins causing impaired p53 binding to its specific promoters (I) and/or p53 degradation through RING proteins (II). (Right) Under stress conditions, enhanced p53 protein levels and activity could be additionally regulated through interaction with MAGE-A/HDAC complex, therefore affecting the acetylation of p53 and histones surrounding p53-binding sites (III).

that cytoplasmic expression of MAGE correlates with reduced number of p53-positive nuclei. Since reduced nuclear p53 is linked to impaired p53 function, this observation supports a role of MAGE proteins in disrupting the p53-dependet response in thyroid carcinomas [36]. Moreover, the role of MAGE-I proteins in multiple myeloma (MM) was studied by analyzing MAGE-A3 expression by immunohistochemistry in samples from two groups of patients representing different stages of the disease [37]. Expression of MAGE-A3 was higher in patients who had relapsed after chemotherapy in comparison with newly diagnosed untreated patients, suggesting a pathogenic role of MAGE-A proteins in progression of MM disease. Furthermore, silencing of MAGE-A proteins was shown to trigger apoptosis in proliferating myeloma cells through p53-dependent up-regulation of Bax and down-regulation of Survivin, a regulator of the mitotic spindle checkpoint. These data suggest that MAGE-A proteins are critical for MM proliferating cells and highlight the relevance of MAGE/p53 relationship. In addition a key role of MAGE-A2 in the inactivation of p53 in head and neck squamous cell carcinoma was reported [38].

It is interesting to consider that, although little information about MAGE-II protein function is available, NECDIN and MAGE-D1 could perform cellular functions opposite to MAGE-I proteins. In this respect, it was reported that NECDIN behaves as a neuron-specific growth suppressor that interacts with p53 and E2F1 transcription factors [39,40]. On the other hand, MAGE-D1 (also known as NRAGE or DLXIN-1) may regulate a variety of proteins that arrest cell growth or induce apoptosis. For example, it was reported that MAGE-D1 activates p53 transcriptional activity [41]. In addition, MAGE-D1 stabilizes BRCA-2 to arrest cell growth [42] and induces apoptosis through p75NTR [43], bone morphogenetic protein signaling [44] and CHE-1 anti-apoptotic protein degradation [45]. Therefore, some MAGE-II proteins could counteract the activity of specific MAGE-I members and vice versa, a worth studying fact which could represent a novel view of MAGE proteins network function.

## 3. MAGE-I sequence homology and function

Due to their high level of sequence homology, MAGE-A proteins could be a priori considered as functionally redundant proteins. However, studies performed in the last years strongly suggest that some MAGE proteins could participate in specific cellular pathways. In this respect, Monte et al. [23] observed that different MAGE-A proteins, such as MAGE-A1, A2 and A6, are able to repress p53 transcriptional activity. However, MAGE-A2 is a p53 stronger repressor than MAGE-A1 and MAGE-A6, suggesting there is a certain degree of functional specificity. In line with this, Peche et al. [33] reported that MAGE-A2 restrains cellular senescence by repressing PMLIV-induced p53 activation at NBs, a function which is not shared by MAGE-A4. Indeed, MAGE-A2 but not MAGE-A4 is able to interact with PMLIV, co-localize with p53 at NBs and affect p53 acetylation status. In line with this data, MAGE-A4 is the only MAGE-A protein associated with pro-apoptotic activities instead of survival [46–49]. The functional specificity of MAGE-A proteins could be due to sequence differences in their less conserved regions (mainly N-terminal) as well as small variations within their conserved MHD. Concerning this last point, Laduron et al. describes a 14 amino acid long C-terminal sequence responsible for MAGE-A1- SKIP1 association [50]. As reported by the authors, this sequence is also present in MAGE-A4 but not in other MAGE-A members. As a consequence, MAGE-A10 was not able to interact with SKIP1 under the same conditions [50].

Another illustration of functional specificity due to sequence differences could be obtained from MAGE-A11 studies, the most deeply characterized MAGE-A sequence at the functional level [51,52]. MAGE-A11 is a co-regulator of the androgen receptor (AR), a ligand-activated transcriptional factor activated by testosterone and dihidrotestosterone [53]. Once activated, AR translocates into the nucleus, interacts with co-regulatory proteins and activates the transcription of its target genes. Of relevance, AR is often activated in prostate cancer cells [54]. MAGE-A11 is able to bind the AR N-terminal FXXLF motif and modulate its N- and C-terminal N/C interaction in the absence of androgen. This raises AR transcriptional activity by increasing accessibility of the AR AF2 region (Activation function 2) and recruitment of co-activators [53]. MAGE-A11-AR interaction is mediated by the MAGE-A11 F-box (residues 329–369), a hydrophobic repeat similar to cyclin-F F-box and conserved throughout the MAGE family. Besides, MAGE-A11 contains a MXXIF (residues 185–189) and a FXXIF motif (residues 260–264) through which interacts with the AR co-activators p300 and TIF2, respectively [51,55]. The FXXIF motif is conserved

among most of MAGE-A proteins and is also present in some MAGE-B proteins. However, the MXXIF motif seems to be functionally specific for MAGE-A11, thus, the interaction with p300 could be a unique feature of MAGE-A11.

Moreover, it has been reported that MAGE-A11 post-translational modifications stabilize MAGE-A11-AR interaction and increase AR transcriptional activity. For example, Epidermal Growth Factor induces MAGE-A11 phosphorylation at Thr-360 and subsequent monoubiquitinylation of Lys-240 and Lys-245 [52]. These three residues are located within the MHD, however, differences in their conservation among MAGE-I proteins can be observed. Thr-360 is conserved within the MAGE-A, MAGE-B and MAGE-C groups, with the exception of MAGE-A2. Lys-245 is conserved among members of the MAGE-A and MAGE-B groups (but not MAGE-C) meanwhile Lys-240 is less conserved, being only present in some MAGE-A and MAGE-B proteins. Such similarities and differences in the conservation of specific amino acids suggest common regulatory mechanisms for some but not all MAGE-I proteins. In addition, after serum stimulation ERK phosphorylates MAGE-A11 at Ser-174, a residue conserved among all MAGE-A proteins but not in MAGE-B and MAGE-C proteins [51].

Recently, a mutational analysis of the coding region of MAGE-I family members revealed that these genes are frequently mutated in tumors [56]. This, together with the relevance of site specific post-translational modifications as well as the existence of functional conserved motifs within the MAGE sequence, opens a further possibility of mutations resulting in changes of MAGE functionality.

## 4. Regulation of MAGE gene expression by p53

Experimental data suggest that p53 could be indirectly involved in the regulation of MAGE protein expression through different mechanisms. One is the case of BORIS, a CTA that exhibits extensive homology to the central region of CTCF, a site-specific chromatin binding factor that regulates transcription through epigenetic control. BORIS and CTCF recognize the same DNA binding sequence but recruit different regulatory proteins since their N- and C-terminal region differs [57]. Unlike CTCF, BORIS binding to DNA can activate CTAs such as *MAGE-I* and *NY-ESO* [8,58]. While CTCF occupies methylated and silenced *MAGE* promoters, activation and demethylation of these promoters result in a complete exchange of CTCF for BORIS, with the consequent enhancement of *MAGE* and other CTAs gene expression. In normal testis, BORIS gene is transcribed from three different promoters; however, some cancer cells mostly use a couple of them. Interestingly, p53 is able to negatively regulate BORIS transcription from all three promoters. No binding of p53 to BORIS promoter was detected, indicating that, as frequently observed, down-regulation of gene expression through p53 is not always mediated by direct binding to DNA [59]. Even if *MAGE-I* expression could not exclusively depend on BORIS function [60],p53 could potentially regulate *MAGE-I* expression by controlling *BORIS* transcription.

Furthermore, p53 can indirectly regulate gene expression through mechanisms involving non-coding RNAs (micro-RNAs, miRNAs). For example, p53 can transcriptionally induce RNAs of the miR-34 family to exert part of its tumor-suppressor function [61]. It has been recently demonstrated that miR-34a targets the 3′UTR mRNA of *MAGE-A* genes [62]. Besides, miR-34a expression represses *MAGE-A* genes and activates p53. Activation of p53 could be in part induced by down-regulation of *MAGE-A* genes as well as by other miR-34 targets [63]. Accordingly, miR-34a has been shown to enhance sensitivity to chemotherapeutic agents in a variety of tumor cells [64].

## 5. New approaches for cancer therapies

MAGE-I proteins are expressed in various humans cancers in a linage-independent fashion [65]. Thus, interfering with MAGE expression or function could have an impact on treatment of a wide range of human cancers, especially those harboring wild type p53.

Considering the HDAC requirement for p53 inhibition through MAGE-A proteins [23], the use of HDAC inhibitors in combination with chemotherapeutic drugs could help to restore p53 activity. Actually, HDAC inhibitors have been shown to induce specific changes in gene expression, leading to restoration of silenced genes and influencing a variety of processes such as growth arrest, differentiation, cytotoxicity and induction of apoptosis [66,67]. Specifically, TSA has potent proliferation-inhibitory properties in cancer cells. However, due to its toxicity, costly and inefficient production, alternative HDAC inhibitors have been developed and some of them are being considered in clinical trials [68]. As HDACs are widely express, the profile of cancer-specific HDACs in a given tumor type could gain importance to allow the design of selective inhibitors that target only cancer cells without affecting normal ones. The fact that combined Etoposide-TSA treatment restores the p53 response and reverts chemoresistance in melanoma cells expressing high levels of MAGE-A proteins [23], sets a promising starting point for further investigation.

As described above, MAGE-I proteins cause p53 suppression possibly by both direct binding to p53 or by recruiting HDACs or KAP1 proteins to p53 containing-complexes. Unlike p53, HDACs or KAP1, MAGE proteins are selectively expressed in cancer cells, with the only exception of germinal cells, which are isolated by the hemato-testicular barrier. Inhibition of MAGE interaction with p53, HDACs or KAP1 would therefore be highly specific, turning MAGE-I proteins into attractive therapeutic targets against cancer diseases. In this respect, Bhatia et al. [69] performed a high throughput screening of a compounds library and identified three small molecule inhibitors of KAP1-MAGE interaction and function [69]. Although further studies are required to use these compounds as therapeutic drugs, this approach suggests that research focused on the inhibition of MAGE interactions will be worth performing in order to improve anticancer therapies, by reactivating p53 or other pathways affected by MAGE expression.

## 6. Conclusions

Due to their tumor specific expression pattern, MAGE-I proteins are useful for diagnostic and prognosis of cancer disease. Besides, since their discovery, MAGE-I proteins have being used as immunogens in different clinical trials. Recently, the study of MAGE-I functions has set a promising starting point for their use as chemotherapeutic targets. Of special interest is the relationship between MAGE-I proteins and p53. As described here, different mechanisms and interactors have been proposed to explain how MAGE-I proteins inhibit p53 transcriptional activity. Undoubtedly, this knowledge would help to develop and improve new strategies and therapies against cancer. It is also interesting to consider that, although MAGE-I proteins are highly conserved; growing evidence strongly suggests an important degree of functional specificity. Even if this review is focused on the MAGE/p53 relationship, it is unlikely that the only function of MAGE-I proteins relies on the control of p53. For this reason, the study of MAGE-I protein function presents a big challenge due to the complexity layer set by their wide number of components. Some of them could in fact be functionally redundant while others could not. In addition, MAGE-I associates with proteins that by themselves contain family members or splicing isoforms such as, p53, HDACs, PML and RING

proteins. However, given that we are just starting to unravel the functions of MAGE-I proteins in cancer cells, the identification of groups of MAGE proteins that exert a specific role will represent the key to simplify the understanding of their contribution to cancer biology.

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## References

[1] P. van der Bruggen, C. Traversari, P. Chomez, C. Lurquin, E. De Plaen, B. Van den Eynde, A. Knuth, T. Boon, A gene encoding an antigen recognized by cytolytic T lymphocytes on a human melanoma, Science 254 (1991) 1643–1647.
[2] P.A. Barker, A. Salehi, The MAGE proteins: emerging roles in cell cycle progression, apoptosis, and neurogenetic disease, J. Neurosci. Res. 67 (2002) 705–712.
[3] C. De Smet, A. Loriot, T. Boon, Promoter-dependent mechanism leading to selective hypomethylation within the 5′ region of gene MAGE-A1 in tumor cells, Mol. Cell. Biol. 24 (2004) 4781–4790.
[4] C. De Smet, C. Lurquin, B. Lethe, V. Martelange, T. Boon, DNA methylation is the primary silencing mechanism for a set of germ line- and tumor-specific genes with a CpG-rich promoter, Mol. Cell. Biol. 19 (1999) 7327–7335.
[5] M. Tachibana, J. Ueda, M. Fukuda, N. Takeda, T. Ohta, H. Iwanari, T. Sakihama, T. Kodama, T. Hamakubo, Y. Shinkai, Histone methyltransferases G9a and GLP form heteromeric complexes and are both crucial for methylation of euchromatin at H3-K9, Genes. Dev. 19 (2005) 815–826.
[6] M. Tachibana, K. Sugimoto, M. Nozaki, J. Ueda, T. Ohta, M. Ohki, M. Fukuda, N. Takeda, H. Niida, H. Kato, Y. Shinkai, G9a histone methyltransferase plays a dominant role in euchromatic histone H3 lysine 9 methylation and is essential for early embryogenesis, Genes. Dev. 16 (2002) 1779–1791.
[7] S.R. James, P.A. Link, A.R. Karpf, Epigenetic regulation of X-linked cancer/germline antigen genes by DNMT1 and DNMT3b, Oncogene 25 (2006) 6975–6985.
[8] S. Vatolin, Z. Abdullaev, S.D. Pack, P.T. Flanagan, M. Custer, D.I. Loukinov, E. Pugacheva, J.A. Hong, H. Morse 3rd, D.S. Schrump, J.I. Risinger, J.C. Barrett, V.V. Lobanenkov, Conditional expression of the CTCF-paralogous transcriptional factor BORIS in normal cells results in demethylation and derepression of MAGE-A1 and reactivation of other cancer-testis genes, Cancer Res. 65 (2005) 7751–7762.
[9] B. Yang, S. O'Herrin, J. Wu, S. Reagan-Shaw, Y. Ma, M. Nihal, B.J. Longley, Select cancer testes antigens of the MAGE-A, -B, and -C families are expressed in mast cell lines and promote cell viability in vitro and in vivo, J. Invest. Dermatol. 127 (2007) 267–275.
[10] F. Gaudet, J.G. Hodgson, A. Eden, L. Jackson-Grusby, J. Dausman, J.W. Gray, H. Leonhardt, R. Jaenisch, Induction of tumors in mice by genomic hypomethylation, Science 300 (2003) 489–492.
[11] K.C. Shin, E.Y. Choi, J.H. Chung, C. Jeon, K.H. Lee, Clinical application of MAGE A1-6 RT-nested PCR for diagnosis of lung cancer invisible by bronchoscopy, Anticancer Res. 32 (2012) 163–167.
[12] Y.M. Hussein, A.F. Ghareib, R.H. Mohamed, M.I. Radwan, W.H. Elsawy, MAGE-3 and MAGE-4 genes as possible markers for early detection of metastases in hepatitis C virus Egyptian patients complicated by hepatocellular carcinoma, Med. Oncol. (2011).
[13] H. Kim, S.J. Kim, S.H. Lee, H.S. Seong, K.O. Lee, C.H. Jeon, Y.J. Hong, S.M. Lee, T.H. Kim, Usefulness of melanoma antigen (MAGE) gene analysis in tissue samples from percutaneous needle aspiration biopsy of suspected lung cancer lesions, Lung Cancer 69 (2010) 284–288.
[14] O.L. Caballero, Y.T. Chen, Cancer/testis (CT) antigens: potential targets for immunotherapy, Cancer Sci. 100 (2009) 2014–2021.
[15] B. Yang, S.M. O'Herrin, J. Wu, S. Reagan-Shaw, Y. Ma, K.M. Bhat, C. Gravekamp, V. Setaluri, N. Peters, F.M. Hoffmann, H. Peng, A.V. Ivanov, A.J. Simpson, B.J. Longley, MAGE-A, mMAGE-b, and MAGE-C proteins form complexes with KAP1 and suppress p53-dependent apoptosis in MAGE-positive cell lines, Cancer Res. 67 (2007) 9954–9962.
[16] W. Liu, S. Cheng, S.L. Asa, S. Ezzat, The melanoma-associated antigen A3 mediates fibronectin-controlled cancer progression and metastasis, Cancer Res. 68 (2008) 8104–8112.
[17] M. Sang, Y. Lian, X. Zhou, B. Shan, MAGE-A family: attractive targets for cancer immunotherapy, Vaccine 29 (2011) 8496–8500.
[18] C.J. Sherr, J.D. Weber, The ARF/p53 pathway, Curr. Opin. Genet. Dev. 10 (2000) 94–99.
[19] E.S. Helton, X. Chen, P53 modulation of the DNA damage response, J. Cell Biochem. 100 (2007) 883–896.
[20] K.H. Vousden, D.P. Lane, P53 in health and disease, Nat. Rev. Mol. Cell. Biol. 8 (2007) 275–283.
[21] A. Petitjean, E. Mathe, S. Kato, C. Ishioka, S.V. Tavtigian, P. Hainaut, M. Olivier, Impact of mutant p53 functional properties on TP53 mutation patterns and tumor phenotype: lessons from recent developments in the IARC TP53 database, Hum. Mutat. 28 (2007) 622–629.
[22] A.J. Levine, The common mechanisms of transformation by the small DNA tumor viruses: the inactivation of tumor suppressor gene products: p53, Virology 384 (2009) 285–293.
[23] M. Monte, M. Simonatto, L.Y. Peche, D.R. Bublik, S. Gobessi, M.A. Pierotti, M. Rodolfo, C. Schneider, MAGE-A tumor antigens target p53 transactivation function through histone deacetylase recruitment and confer resistance to chemotherapeutic agents, Proc. Natl. Acad. Sci. USA 103 (2006) 11160–11165.
[24] C. Wang, A. Ivanov, L. Chen, W.J. Fredericks, E. Seto, F.J. Rauscher 3rd, J. Chen, MDM2 interaction with nuclear corepressor KAP1 contributes to p53 inactivation, Embo. J. 24 (2005) 3279–3290.
[25] C. Wang, F.J. Rauscher 3rd, W.D. Cress, J. Chen, Regulation of E2F1 function by the nuclear corepressor KAP1, J. Biol. Chem. 282 (2007) 29902–29909.
[26] J.M. Doyle, J. Gao, J. Wang, M. Yang, P.R. Potts, MAGE-RING protein complexes comprise a family of E3 ubiquitin ligases, Mol. Cell. 39 (2010) 963–974.
[27] A.V. Ivanov, H. Peng, V. Yurchenko, K.L. Yap, D.G. Negorev, D.C. Schultz, E. Psulkowski, W.J. Fredericks, D.E. White, G.G. Maul, M.J. Sadofsky, M.M. Zhou, F.J. Rauscher 3rd, PHD domain-mediated E3 ligase activity directs intramolecular sumoylation of an adjacent bromodomain required for gene silencing, Mol. Cell. 28 (2007) 823–837.
[28] Y. Feng, J. Gao, M. Yang, When MAGE meets RING: insights into biological functions of MAGE proteins, Protein Cell 2 (2011) 7–12.
[29] L. Marcar, N.J. Maclaine, T.R. Hupp, D.W. Meek, MAGE-A cancer/testis antigens inhibit p53 function by blocking its interaction with chromatin, Cancer Res. 70 (2010) 10362–10370.
[30] K.H. Vousden, C. Prives, Blinded by the light: the growing complexity of p53, Cell 137 (2009) 413–431.
[31] B. Liu, Y. Chen, D.K. St Clair, ROS and p53: a versatile partnership, Free Radic. Biol. Med. 44 (2008) 1529–1535.
[32] M.F. Ladelfa, M.F. Toledo, J.E. Laiseca, M. Monte, Interaction of p53 with tumor suppressive and oncogenic signaling pathways to control cellular reactive oxygen species production, Antioxid. Redox. Sig. 15 (2011) 1749–1761.
[33] L.Y. Peche, M. Scolz, M.F. Ladelfa, M. Monte, C. Schneider, MageA2 restrains cellular senescence by targeting the function of PMLIV/p53 axis at the PML-NBs, Cell. Death Differ. (2011).
[34] R. Kepkay, K.M. Attwood, Y. Ziv, Y. Shiloh, G. Dellaire, KAP1 depletion increases PML nuclear body number in concert with ultrastructural changes in chromatin, Cell Cycle 10 (2011) 308–322.
[35] Y. Ziv, D. Bielopolski, Y. Galanty, C. Lukas, Y. Taya, D.C. Schultz, J. Lukas, S. Bekker-Jensen, J. Bartek, Y. Shiloh, Chromatin relaxation in response to DNA double-strand breaks is modulated by a novel ATM- and KAP1 dependent pathway, Nat. Cell. Biol. 8 (2006) 870–876.
[36] S. Cheng, W. Liu, M. Mercado, S. Ezzat, S.L. Asa, Expression of the melanoma-associated antigen is associated with progression of human thyroid cancer, Endocr. Relat. Cancer 16 (2009) 455–466.
[37] T. Nardiello, A.A. Jungbluth, A. Mei, M. Diliberto, X. Huang, A. Dabrowski, V.C. Andrade, R. Wasserstrum, S. Ely, R. Niesvizky, R. Pearse, M. Coleman, D.S. Jayabalan, N. Bhardwaj, L.J. Old, S. Chen-Kiang, H.J. Cho, MAGE-A inhibits apoptosis in proliferating myeloma cells through repression of Bax and maintenance of survivin, Clin. Cancer Res. 17 (2011) 4309–4319.
[38] C.A. Glazer, I.M. Smith, S. Bhan, W. Sun, S.S. Chang, K.M. Pattani, W. Westra, Z. Khan, J.A. Califano, The role of MAGEA2 in head and neck cancer, Arch. Otolaryngol. Head Neck Surg. 137 (2011) 286–293.
[39] H. Taniura, K. Matsumoto, K. Yoshikawa, Physical and functional interactions of neuronal growth suppressor necdin with p53, J. Biol. Chem. 274 (1999) 16242–16248.
[40] H. Taniura, N. Taniguchi, M. Hara, K. Yoshikawa, NECDIN, a postmitotic neuron-specific growth suppressor, interacts with viral transforming proteins and cellular transcription factor E2F1, J. Biol. Chem. 273 (1998) 720–728.
[41] C.J. Wen, B. Xue, W.X. Qin, M. Yu, M.Y. Zhang, D.H. Zhao, X. Gao, J.R. Gu, C.J. Li, HNRAGE, a human neurotrophin receptor interacting MAGE homologue, regulates p53 transcriptional activity and inhibits cell proliferation, FEBS Lett. 564 (2004) 171–176.
[42] X.X. Tian, D. Rai, J. Li, C. Zou, Y. Bai, D. Wazer, V. Band, Q. Gao, BRCA2 suppresses cell proliferation via stabilizing MAGE-D1, Cancer Res. 65 (2005) 4747–4753.
[43] A.H. Salehi, P.P. Roux, C.J. Kubu, C. Zeindler, A. Bhakar, L.L. Tannis, J.M. Verdi, P.A. Barker, NRAGE, a novel MAGE protein, interacts with the p75 neurotrophin receptor and facilitates nerve growth factor-dependent apoptosis, Neuron 27 (2000) 279–288.
[44] S.E. Kendall, C. Battelli, S. Irwin, J.G. Mitchell, C.A. Glackin, J.M. Verdi, NRAGE mediates p38 activation and neural progenitor apoptosis via the bone morphogenetic protein signaling cascade, Mol. Cell. Biol. 25 (2005) 7711–7724.
[45] M.G. Di Certo, N. Corbi, T. Bruno, S. Iezzi, F. De Nicola, A. Desantis, M.T. Ciotti, E. Mattei, A. Floridi, M. Fanciulli, C. Passananti, NRAGE associates with the anti-apoptotic factor Che-1 and regulates its degradation to induce cell death, J. Cell. Sci. 120 (2007) 1852–1858.
[46] T. Sakurai, K. Itoh, H. Higashitsuji, T. Nagao, K. Nonoguchi, T. Chiba, J. Fujita, A cleaved form of MAGE-A4 binds to Miz-1 and induces apoptosis in human cells, J. Biol. Chem. 279 (2004) 15505–15514.

[47] T. Nagao, H. Higashitsuji, K. Nonoguchi, T. Sakurai, S. Dawson, R.J. Mayer, K. Itoh, J. Fujita, MAGE-A4 interacts with the liver oncoprotein gankyrin and suppresses its tumorigenic activity, J. Biol. Chem. 278 (2003) 10668–10674.
[48] T. Sakurai, M. Kudo, K. Itoh, U. Ryu, H. Higashitsuji, J. Fujita, Adriamycin enhances proteasome-mediated generation of the proapoptotic processed form of MAGE-A4 in hepatoma cells, Oncology 81 (Suppl 1) (2011) 30–35.
[49] T. Peikert, U. Specks, C. Farver, S.C. Erzurum, S.A. Comhair, Melanoma antigen A4 is expressed in non-small cell lung cancers and promotes apoptosis, Cancer Res. 66 (2006) 4693–4700.
[50] S. Laduron, R. Deplus, S. Zhou, O. Kholmanskikh, D. Godelaine, C. De Smet, S.D. Hayward, F. Fuks, T. Boon, E. De Plaen, MAGE-A1 interacts with adaptor SKIP and the deacetylase HDAC1 to repress transcription, Nucl. Acids Res. 32 (2004) 4340–4350.
[51] E.B. Askew, S. Bai, A.T. Hnat, J.T. Minges, E.M. Wilson, Melanoma antigen gene protein-A11 (MAGE-11) F-box links the androgen receptor NH2-terminal transactivation domain to p160 coactivators, J. Biol. Chem. 284 (2009) 34793–34808.
[52] S. Bai, E.M. Wilson, Epidermal-growth-factor-dependent phosphorylation and ubiquitinylation of MAGE-11 regulates its interaction with the androgen receptor, Mol. Cell. Biol. 28 (2008) 1947–1963.
[53] S. Bai, B. He, E.M. Wilson, Melanoma antigen gene protein MAGE-11 regulates androgen receptor function by modulating the interdomain interaction, Mol. Cell. Biol. 25 (2005) 1238–1257.
[54] J.L. Mohler, C.W. Gregory, O.H. Ford 3rd, D. Kim, C.M. Weaver, P. Petrusz, E.M. Wilson, F.S. French, The androgen axis in recurrent prostate cancer, Clin. Cancer Res. 10 (2004) 440–448.
[55] E.B. Askew, S. Bai, A.J. Blackwelder, E.M. Wilson, Transcriptional synergy between melanoma antigen gene protein-A11 (MAGE-11) and p300 in androgen receptor signaling, J. Biol. Chem. 285 (2010) 21824–21836.
[56] O.L. Caballero, Q. Zhao, D. Rimoldi, B.J. Stevenson, S. Svobodova, S. Devalle, U.F. Rohrig, A. Pagotto, O. Michielin, D. Speiser, J.D. Wolchok, C. Liu, T. Pejovic, K. Odunsi, F. Brasseur, B.J. Van den Eynde, L.J. Old, X. Lu, J. Cebon, R.L. Strausberg, A.J. Simpson, Frequent MAGE mutations in human melanoma, PLoS One 5 (2010).
[57] E.M. Klenova, H.C. Morse 3rd, R. Ohlsson, V.V. Lobanenkov, The novel BORIS + CTCF gene family is uniquely involved in the epigenetics of normal biology and cancer, Semin. Cancer Biol. 12 (2002) 399–414.
[58] J.A. Hong, Y. Kang, Z. Abdullaev, P.T. Flanagan, S.D. Pack, M.R. Fischette, M.T. Adnani, D.I. Loukinov, S. Vatolin, J.I. Risinger, M. Custer, G.A. Chen, M. Zhao, D.M. Nguyen, J.C. Barrett, V.V. Lobanenkov, D.S. Schrump, Reciprocal binding of CTCF and BORIS to the NY-ESO-1 promoter coincides with derepression of this cancer-testis gene in lung cancer cells, Cancer Res. 65 (2005) 7763–7774.
[59] S. Renaud, D. Loukinov, F.T. Bosman, V. Lobanenkov, J. Benhattar, CTCF binds the proximal exonic region of hTERT and inhibits its transcription, Nucl. Acids Res. 33 (2005) 6850–6860.
[60] A. Woloszynska-Read, S.R. James, C. Song, B. Jin, K. Odunsi, A.R. Karpf, BORIS/CTCFL expression is insufficient for cancer-germline antigen gene expression and DNA hypomethylation in ovarian cell lines, Cancer Immun. 10 (2010) 6.
[61] L. He, X. He, L.P. Lim, E. de Stanchina, Z. Xuan, Y. Liang, W. Xue, L. Zender, J. Magnus, D. Ridzon, A.L. Jackson, P.S. Linsley, C. Chen, S.W. Lowe, M.A. Cleary, G.J. Hannon, A microRNA component of the p53 tumour suppressor network, Nature 447 (2007) 1130–1134.
[62] S.D. Weeraratne, V. Amani, A. Neiss, N. Teider, D.K. Scott, S.L. Pomeroy, Y.J. Cho, MiR-34a confers chemosensitivity through modulation of MAGE-A and p53 in medulloblastoma, Neur. Oncol. 13 (2010) 165–175.
[63] M. Yamakuchi, M. Ferlito, C.J. Lowenstein, MiR-34a repression of SIRT1 regulates apoptosis, Proc. Natl. Acad. Sci. USA 105 (2008) 13421–13426.
[64] H. Hermeking, The miR-34 family in cancer and apoptosis, Cell Death Differ. 17 (2010) 193–199.
[65] M. Sang, L. Wang, C. Ding, X. Zhou, B. Wang, L. Wang, Y. Lian, B. Shan, Melanoma-associated antigen genes – an update, Cancer Lett. 302 (2011) 85–90.
[66] L. Ellis, Y. Pan, G.K. Smyth, D.J. George, C. McCormack, R. Williams-Truax, M. Mita, J. Beck, H. Burris, G. Ryan, P. Atadja, D. Butterfoss, M. Dugan, K. Culver, R.W. Johnstone, H.M. Prince, Histone deacetylase inhibitor panobinostat induces clinical responses with associated alterations in gene expression profiles in cutaneous T-cell lymphoma, Clin. Cancer Res. 14 (2008) 4500–4510.
[67] J. Joseph, G. Mudduluru, S. Antony, S. Vashistha, P. Ajitkumar, K. Somasundaram, Expression profiling of sodium butyrate (NaB)-treated cells: identification of regulation of genes related to cytokine signaling and cancer metastasis by NaB, Oncogene 23 (2004) 6304–6315.
[68] I. Hoshino, H. Matsubara, Recent advances in histone deacetylase targeted cancer therapy, Surg. Today 40 (2010) 809–815.
[69] N. Bhatia, B. Yang, T.Z. Xiao, N. Peters, M.F. Hoffmann, B.J. Longley, Identification of novel small molecules that inhibit protein–protein interactions between MAGE and KAP1, Arch. Biochem. Biophys. 508 (2011) 217–221.