The MAGE proteins are best known as curious tumor-specific antigens. However, Doyle et al. (2010) reveal that MAGE proteins interact with RING proteins to promote ubiquitylation which provides important new insights into the physiological and pathological functions of this enigmatic family of proteins.
consistent with previous studies, which show that MAGE I binding to TRIM28 suppresses p53-dependent apoptosis in tumor cells (Yang et al., 2007).

An open question is how MAGE interactions at distal sites enhance RING-mediated substrate ubiquitylation. A tantalizing hint is that MAGE-C2 also binds directly to UBCH2, the same E2 ubiquitin ligase that interacts with TRIM28. It remains to be determined whether MAGE-C2’s MHD domain is also required for its interaction with UBCH2. An attractive model is that a trifecta of interactions between TRIM28, UBCH2, and MAGE-C2 favors on-site recharging of UBCH2. This would potentially enable UBCH2 to dissociate from the RING and be recharged by an E1 (E2 interactions with E3s and E1s are mutually exclusive) (Deshaies and Joazeiro, 2009) while remaining stably bound to TRIM28 through interactions with MAGE-C2 (Figure 1B). Alternatively, TRIM28 may recruit two UBCH2 molecules, one via its RING domain and another via MAGE-C2, to promote the sequential assembly of a polyubiquitin chain (Deshaies and Joazeiro, 2009) on the active site of UBCH2 that is transferred en bloc to p53. This may also help to explain why the MAGE MHDs interact with RING proteins via domains other than the RING, especially if such interactions evolved subsequent to the convergence of MAGEs and their RING partners.

Figure 1. The Conserved MAGE I and II MHD Domains Interact with Variable Domains in RING Proteins to Promote the Ubiquitylation of Substrates, such as p53, which May Play an Important Role in Their Physiological and Pathological Functions

(A) The conserved MAGE homology domain (MHD) comprises two winged helices connected by a flexible linker region. MAGE I gene expression is normally limited to germ cells but becomes aberrantly expressed in many tumors. MAGE II genes are expressed in many different somatic tissues. A unifying theme is that MAGE I and II MHDs interact with variable domains in RING finger E3 ubiquitin ligases to form novel protein complexes that may promote ubiquitylation.

(B) A model for how MAGE-C2 interactions with TRIM28 (an E3 ligase) and UBCH2 (an E2 ligase) promote the ubiquitylation of the tumor suppressor protein, p53, which may play an important physiological role in germ cell survival and pathological role in tumor survival and resistance to therapy. In addition to the MAGE I-RING interactions identified in this study, genome-wide yeast two-hybrid (Y2H) screens (Rual et al., 2005) have also identified MAGE-RING protein-protein interactions (right) that could play a novel role in regulating protein turnover to promote germ cell and tumor maintenance.
on the same E2s. MAGE genes have also been identified in Drosophila, Aspergillis, and Arabidopsis, which could provide important insights regarding the ancestral interactions and functions of the MHD and when their interactions with RING proteins and E2s first arose. This study fundamentally changes how we look at MAGE proteins as a whole, from curious antigens expressed on tumor cells and in the testis to novel modulators of protein homeostasis. A key question is whether MAGE I-RING interactions promote the ubiquitylation of critical substrates that confer germ cell maintenance but aberrant tumor survival. In this regard, it is interesting to note the many striking similarities that exist between germ cells and tumor cells, including their enhanced migratory and invasive properties and the ability to tolerate cyclic changes in ploidy (Simpson et al., 2005). In tumor cells, the normal complement of RING protein partners and substrates is also likely to differ, resulting in potential gain-of-function interactions between MAGEs and RINGs that may have completely unprecedented activities and pathologies. The interaction of MAGE-C2 with TRIM28 to enhance p53 degradation may also be of great clinical significance in rendering tumor cells refractory to irradiation, chemotherapy, and small molecule antagonists of MDM2. Finally, consistent with the conclusions of Doyle et al., genome-wide yeast two-hybrid studies have also identified novel interactions between MAGEs and RING proteins (Rual et al., 2005), which will be interesting to explore in this new context (Figure 1B). Many of the novel RING partners identified are members of the TRIM family that, similar to the MAGEs, underwent a vast expansion during mammalian evolution (Sardiello et al., 2008). It is intriguing to speculate that the expansion of both of these families of proteins and their potentially novel interactions with each other may have provided the subtleties and activities that not only make us uniquely human, but also refractory to therapy when cancer arises.

REFERENCES


