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The MAGE protein family: Protein degradation, genome stability, and cancer

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Cancer-testis antigens (CTAs), including the MAGE protein family, are genes whose expression is typically restricted to the germline, but are aberrantly expressed and presented as antigens in human tumors. Surprising recent evidence suggests that the aberrant expression of MAGE CTAs in tumors is not simply an inert consequence of widespread genomic deregulation, but rather an important functional event promoting tumorigenesis. Furthermore, the expression of MAGE CTAs correlates with poor prognosis in a variety of cancer types. However, the mechanism through which MAGE CTAs promote tumorigenesis has been enigmatic. In this study, we investigated the biochemical and cellular function of the large MAGE protein family comprising more than 60 members, many of which are CTAs. Using a variety of *in vitro* and cellular assays, we identified common binding partners of more than ten MAGE proteins, solved the crystal structure of one MAGE protein, investigated the biochemical activity of MAGEs, and discovered a cellular function of several MAGE CTAs relevant to their oncogenic activity. We found that a common feature of MAGE proteins is their ability to bind to and enhance the activity of E3 RING ubiquitin ligases, such TRIM28/KAP1, through a conserved tandem winged-helix domain. Importantly, we show that several MAGE-TRIM28 ubiquitin ligase complexes directly ubiquitylate and degrade the critical p53 tumor suppressor. Thus, we have identified a novel, cancer-specific regulator of p53 degradation and discovered the function of the enigmatic MAGE protein family. These results underscore the importance of MAGE proteins as therapeutic targets for cancer.

Biography

Ryan Potts obtained his B.S. from the University of North Carolina in 2000. In 2003 he entered into the Cell Regulation Ph.D. program at UT Southwestern Medical Center under the mentorship of Hongtao Yu in the department of Pharmacology. He completed his dissertation in 2007 studying the molecular and biochemical processes that safeguard the genome. Afterward, he stayed on at UT Southwestern Medical Center as an independent investigator in the department of Biochemistry as a Sara and Frank McKnight fellow. Currently, his research is focused on understanding the basic molecular, genetic, and cellular events that give rise to cancer.