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## Should MAGE be the rage in myeloma?

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role of PI3K in cell adhesion, they found the expected result that neutrophil adhesion to the endothelium was markedly impaired in PI3K $\gamma$  and PI3K $\delta$  knockout mice. Remarkably, they found that wild-type neutrophils were also impaired in their ability to adhere to PI3K $\gamma$  knockout endothelial cells. This demonstrates the importance of a PI3K $\gamma$ -dependent signaling cascade within endothelial cells, that is, cells required for their adhesion to neutrophils. Puri and colleagues speculate that endothelial cell PI3K $\gamma$  is required for an endothelial cell adhesion receptor, E-selectin, to tether neutrophils. Although at this point, other possible explanations still exist.

In addition to chemotaxis and adhesion, PI3Ks are involved in diverse cellular events, including the prevention of apoptosis, regulation of glucose metabolism, and cell proliferation. Lessons from pharmacologic inhibitors, knockout mice, and single-cell microscopy studies have advanced our knowledge of these processes considerably over the past few years.

The challenge will be to inhibit specific PI3K isoforms in discreet regions of cells to target migration without affecting other PI3K-dependent processes. ■

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between MAGE-A3/6 and plasma cell proliferation at all stages of disease suggests that this antigen might play a formative role in tumorigenesis.

The investigators correlated expression, using polymerase chain reaction and immunohistochemistry, with proliferation using a plasma cell proliferative index (PCPI) measured on the CD138<sup>+</sup> population. Protein expression was seen in more than 70% of the myeloma samples tested, with even higher levels of mRNA expression. Although CD138<sup>+</sup> cells comprise the bulk of the tumor in myeloma, based on work by Matsui et al,<sup>4</sup> they lack the ability to self-renew and differentiate into plasma cells. Rather, there is a small population of CD138<sup>-</sup>/CD20<sup>+</sup> myeloma cells that appears to be “myeloma stem cells.” These cells have the ability to replicate, self-renew, and differentiate into mature myeloma plasma cells.<sup>4</sup> The current study did not analyze CT7 and MAGE A3/6 expression by the CD138<sup>-</sup>/CD20<sup>+</sup> myeloma cells. If, in fact, these proteins are not expressed by the myeloma “stem cell,” then even a highly effective vaccine, in terms of clinical response, is unlikely to eradicate myeloma. Alternatively, if these proteins are expressed by the myeloma “stem cell,” an effective vaccine could eliminate both the differentiated plasma cells and the immature stem cell leading to eradication of the disease.

Nonetheless, the ability to target these antigens immunologically or through small molecules designed to interrupt their function could have important clinical consequences, not only for therapy but for the ability to detect minimal residual disease. We anxiously await future studies looking at the expression of these proteins in myeloma stem cells and in immunobiologically based strategies involving these antigens. ■

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Comment on Jungbluth et al, page 167

## Should MAGE be the rage in myeloma?

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Jungbluth and colleagues have identified 2 cancer testis antigens as potential diagnostic and therapeutic targets in multiple myeloma.

**D**espite the advent of mechanistically diverse agents with important clinical efficacy, multiple myeloma remains an incurable disease. Insights into the biology of aberrant plasma cell differentiation in monoclonal gammopathy of undetermined significance (MGUS) and myeloma offer the potential for new therapeutic strategies. Immunologic antitumor approaches, in particular T-cell-mediated responses, have been shown to be efficacious in patients with myeloma.<sup>1-3</sup> Unfortunately, these responses are neither sensitive nor specific and are ineffective in the majority of patients with myeloma. In an endeavor to develop more potent, targeted responses, many investigators have worked to identify potential targets for immunotherapeutic strategies. Toward this end, Jungbluth and colleagues have identified 2 cancer testis antigens in MGUS and myeloma that may serve as targets for immunotherapeutic strategies.

Cancer testis antigens are attractive targets for vaccine-based therapy, as they are highly immunogenic and appear to have limited expression patterns, being found in gametogenesis and tumor cells, but not in normal tissues. In this edition, the investigators report high levels of expression of CT7 (melanoma antigen C1 [MAGE-C1]) and MAGE-A3/6 in bone marrow samples from patients with MGUS and multiple myeloma, but not in normal plasma cells or non-Hodgkin lymphoma. They have elegantly shown that CT7 expression is higher in myeloma than in MGUS, whereas MAGE-A3/6 expression is present in both MGUS and myeloma, without a change in expression level with higher stages of disease. These data suggest that the proteins are important not only because their expression appears limited to plasma cell dyscrasias, but also because these proteins may be associated with transcriptional regulation and cell-cycle progression. In particular, the apparent link