A new approach to tumor immunotherapy

Homologs of the NKG2D receptor are found in several species, including mouse and human. This receptor is expressed on various cell types, including natural killer (NK) cells, αβ CD8+ T cells, γδ T cells and macrophages. It signals through an associated molecule, DAP10, which recruits and activates the p85 subunit of phosphatidylinositol 3-kinase leading to the ability of cells, such as NK cells, to lyse tumor targets. There are several known ligands for NKG2D, all related distantly to the MHC class I molecules. These include MICA, MICB and ULBP-1, -2 and -3 in the human, and H60 and Rae1-α, -β, -γ and -δ in the mouse. Whereas MICA, MICB, H60 and Rae1 appear to be expressed at a higher level on transformed tissues, such a relationship has yet to be established for the ULBPs. Expression of many of the NKG2D ligands has been associated also with intracellular infection (both viral and bacterial) or stress, such as heat shock. Consistent with this, UL16, a product of human cytomegalovirus, has been reported to bind to MICB, and ULBP-1 and -2, inhibiting their capacity to signal NK-cell activation through NKG2D. This observation implies that NKG2D has an important antiviral role, perhaps in the recognition of virus-infected cells by NK cells.

Given the known capacity of NKG2D ligands H60 and Rae1-β to stimulate NK-cell-mediated lysis of tumor cells in vitro, Raulet and colleagues explored the role of these molecules in the stimulation of tumor immunity in vivo. H60 and Rae1-β were expressed separately on three different tumor cell lines - EL4, B16 and RMA - by transduction with retroviral vectors. These lines were shown to be rejected efficiently by syngeneic hosts; a process mediated primarily by NK cells, although in the case of RMA, also involving CD8+ T cells. Tumor rejection was seen for both H60 and Rae1-β transductants, but not for control transduced cell lines. These data show clearly that such NKG2D ligands are able to stimulate NK-cell-mediated tumor rejection. In addition, all three tumor lines expressing H60 or Rae1-β specifically primed CD8+ T-cell memory responses that were able to reject subsequent challenges with untransduced cell lines. CD8+ T-cell priming was not simply due to NK-cell-mediated tumor destruction, because equivalent destruction by tumor irradiation did not improve immunogenicity. Immunity generated by NKG2D signaling was cell-line specific and