Cancer Immunity (16 May 2007) Vol. 7 Suppl.1, p. 15

CANCER
IMMUNITY
Meeting Abstract

Mechanisms of protective tumor immunity

Glenn Dranoff

Dana-Farber Cancer Institute, Boston, MA, USA

Abstract

Vaccination with irradiated tumor cells engineered to secrete granulocyte-macrophage colony stimulating factor (GM-CSF) enhances tumor immunity in murine models through improved tumor antigen presentation by mature CD11b+ dendritic cells and macrophages. CD4+ and CD8+ T cells, CD1d-restricted invariant NKT cells, and antibodies are required for tumor protection. We have conducted several Phase I clinical trials of this vaccination scheme, using adenoviral mediated gene transfer to engineer autologous tumor cells, in patients with advanced melanoma, non-small lung carcinoma, ovarian carcinoma, and myeloid leukemia. These studies have revealed that vaccination increases tumor immunity in the majority of subjects, as distant metastases become densely infiltrated with T and B cells that accomplish extensive tumor necrosis. Moreover, the administration of a fully human monoclonal antibody that blocks cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) to previously vaccinated patients evokes additional tumor destruction with lymphocyte and granulocyte infiltrates and the disruption of the tumor vasculature.

Unexpectedly, we found that some patients who achieved clinically significant responses to these therapies developed high titer antibodies against MHC class I chain-related protein A (MICA). This NKG2D ligand is frequently expressed on tumor cells as part of the DNA damage response. While the activation of NKG2D on innate and adaptive cytotoxic lymphocytes contributes to immune-mediated tumor destruction, tumor cell shedding of MICA, results in immune suppression through down-regulation of NKG2D surface expression. Nonetheless, we found that the immunotherapy-induced humoral reactions to MICA were associated with a reduction of circulating soluble MICA (sMICA) and an augmentation of NK cell and CD8+ T lymphocyte cytotoxicity. These anti-MICA antibodies efficiently opsonized cancer cells for dendritic cell cross-presentation, which was correlated with a diversification of tumor antigen recognition. The anti-MICA antibodies also accomplished tumor cell lysis through complement fixation. Together, these findings establish a key role for the NKG2D pathway in the clinical activity of CTLA-4 antibody blockade and GM-CSF secreting tumor cell vaccines. Moreover, these results highlight the therapeutic potential of anti-MICA antibodies to overcome immune suppression and effectuate tumor destruction in patients.