

Balancing tumor immunity and autoimmunity

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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. Antibody based-expression cloning technologies have uncovered a large number of novel targets of these vaccine-induced responses, with evidence of a coordinated antigen-specific cellular and humoral reaction.

Despite improved immunity, however, the majority of vaccinated patients eventually succumb to progressive disease. While the evolution of antigen-loss variants presents one obstacle to durable tumor control, negative immune regulation constitutes an additional major challenge. In preliminary clinical studies, 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. CTLA-4 blockade may also breach tolerance to normal tissues, as indicated by the development of autoimmunity. A key issue of ongoing investigation is to determine whether tumor destruction and serious autoimmunity can be dissociated.

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