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Meeting Abstract

GM-CSF based cancer vaccines

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Vaccination with irradiated tumor cells engineered to secrete granulocyte-macrophage colony stimulating factor (GM-CSF) generates potent, specific, and long-lasting anti-tumor immunity in murine models through improved tumor antigen presentation by mature CD11b+ dendritic cells and macrophages. The coordinated activities of CD4+ and CD8+ T cells, CD1d-restricted invariant NKT cells, and antibodies accomplish protective immunity. Two Phase I clinical trials evaluating this immunization scheme in patients with disseminated melanoma revealed the consistent elicitation in distant metastases of dense T- and B-cell infiltrates that effectuated substantial tumor necrosis and fibrosis. In a pilot study of previously vaccinated patients, the subsequent administration of a humanized blocking antibody against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) stimulated additional tumor destruction with lymphocyte and granulocyte infiltrates, albeit with the development of T-cell reactivity to normal melanocytes.

Studies to date established that patients responding to vaccination developed high titer IgG antibodies that were reactive with cell surface and intracellular melanoma determinants as demonstrated by immunoblotting and flow cytometry. Lymphocytes harvested from infiltrated metastases displayed potent cytotoxicity and broad cytokine production towards autologous melanoma cells. Through a combination of antibody-based expression cloning and T-cell epitope characterization, the ATP6S1 subunit of the vacuolar-ATPase complex, the putative opioid growth factor receptor OGFr, and the melanoma inhibitor of apoptosis protein (ML-IAP) were identified as target antigens for antibodies or T cells in some long-term responding patients. Unexpectedly, humoral reactions to ATP6S1 and OGFr were associated with tumor destruction in patients with diverse cancers. Moreover, the delineation of ML-IAP as a target revealed that antigen-loss variants could mediate immune evasion within the context of whole tumor cell vaccines. Additional detailed analysis of blood and tumor samples from responding and resistant patients in these clinical trials should help elucidate the mechanisms and targets of immune-mediated tumor destruction.