

Balancing tumor immunity and inflammation

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Abstract

We demonstrated that 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. Several phase I clinical trials evaluating this immunization scheme in patients with disseminated tumors revealed the consistent elicitation in distant metastases of dense T and B cell infiltrates that effectuated substantial tumor necrosis and fibrosis. Moreover, the subsequent administration of a humanized blocking antibody against cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) accomplished additional tumor destruction with lymphocyte and granulocyte infiltrates in a majority of stage IV patients, in the absence of serious autoimmune toxicities. Detailed study of blood and tumor samples from patients on these trials revealed the induction of a broad cellular and humoral response to multiple tumor-associated antigens, including melanoma inhibitor of apoptosis protein (ML-IAP) and MHC class I chain-related protein A (MICA). Pathologic examination of tumor infiltrates following immunotherapy revealed a linear relationship between the extent of tumor necrosis and the natural logarithm of the ratio of CD8⁺ cytotoxic T cells to FoxP3 expressing regulatory T cells (Tregs).

Our recent investigations of GM-CSF deficient mice uncovered an unexpected critical role for this cytokine in Treg homeostasis. GM-CSF is required for the expression of the phosphatidylserine binding protein milk fat globule EGF-8 (MFG-E8) in antigen presenting cells, whereas the uptake of apoptotic cells by phagocyte-derived MFG-E8 stimulates peripheral Treg maintenance through TGF- β , MHC class II, and CCL22. In wild type mice, MFG-E8 limits the potency of GM-CSF secreting B16 melanoma vaccines through Treg induction, while a dominant negative MFG-E8 mutant (RGE) potentiates therapeutic immunity through Treg inhibition, resulting in the regression of established tumors. Together, these findings suggest that combinations of GM-CSF and MFG-E8 inhibition might improve the efficacy of cancer vaccines and complement the activity of CTLA-4 antibody blockade. Efforts to translate this combinatorial strategy involving MFG-E8 blockade into early stage clinical testing in advanced melanoma patients are underway.