

Overcoming obstacles to the generation of T cells for tumor therapy

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Despite the identification of an increasing number of tumor antigens as a result of the application of powerful molecular methods, and the clear demonstrations that T cells reactive with such antigens can recognize and kill tumor cells, generating therapeutic T-cell responses in patients with malignancies has proven surprisingly difficult. This less than satisfactory outcome reflects the cumulative effects of the obstacles in cancer patients to generating effector cells with adequate avidity in sufficient numbers for tumor eradication, and strategies to overcome these obstacles will be necessary for T cell-based immunotherapies to become reproducibly effective.

Most candidate tumor antigens are self-proteins that are over-expressed by the malignancy, and we have studied three prototypic antigens, WT-1, a pro-oncogenic transcription factor; proteinase 3, a serine protease that degrades selected transcription factors; and MART1, a melanosomal protein. In most patients, CD8+ T cells reactive with these proteins are either naive, having ignored the developing tumor, or have been rendered tolerant to the protein because the antigen has been encountered on normal cells and/or the progressing tumor. We have focused on generating responses to such antigens *in vitro*, in part because this removes the cells from a potentially hostile *in vivo* environment, and in part because it is possible to better dissect and define the components required for a response.

Difficulties generating primary responses *in vitro* have largely reflected the initially low precursor frequency of reactive cells in the naive repertoire, and the limited understanding of the signals required to induce memory cells and effectively expand the responding population. *In vitro* systems that have now overcome these problems will be described. For some tumor antigens that are self-proteins, the reactive cells remaining in the repertoire are of too low avidity to recognize tumor cells, and strategies to improve TCR affinity and functional avidity will be discussed.

Rescuing potentially tumor-reactive CD8+ T cells that have been tolerized in the host and restoring function provides an alternative source of cells that might be used in tumor therapy. A murine model system for isolating and studying large numbers of tolerant cells has been developed, and studies will be presented describing how peripheral tolerance is induced and strategies for rescuing reactive cells that function in tumor therapy.

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