

Integrated analysis of melanoma-T cell interactions in situ; relevance for immunotherapy

Dutch Cancer Society Research grant

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Project number: AMC2006-3606

Clinical studies have shown that immunotherapy of melanoma by vaccination or by adoptive transfer of effector T cells can mediate tumor regression. Autoimmunity against melanocytes (vitiligo) frequently coincided with effective anti-tumor immunity, which indicates that effective immune responses may attack both normal melanocytes and melanoma cells. However, the relatively low frequency of tumor responses in treated patients indicates that the induction of systemic anti-tumor immunity may be insufficient to address the complexity of tumor-host interactions and to achieve a potent anti-tumor effect in most patients.

Our purpose is to establish whether the frequently observed absence of tumor regression in the presence of infiltrating T cells is due to a lack of T cell effector function, caused by impaired imprinting of effector function during T cell priming by activated DC, lack of T cell help or the influence of regulatory T cells, or due to tumor resistance to T cell-mediated lysis.

To discriminate between these processes, we have developed an ex vivo tumor and skin explant system, in which we can test in situ lysis of melanocytes by specific T cells from melanoma patients, which is a measure of T cell function, as well as the capacity of T cells to mediate destruction of melanoma cells, which involves both T cell function and tumor resistance. By comparing melanoma antigen-specific T cells that are isolated from vitiligo lesions and which have proven in vivo efficacy with T cells isolated from melanoma patients, we can answer the question whether autoimmune T cells are more effective in lysing melanoma cells than the T cells that infiltrate in melanomas. Subsequently, we will investigate whether immuno-editing compounds increase the efficacy of melanoma-derived T cells in these assays to the level observed for the autoimmune T cells. Based on the results, we will design specific intervention strategies to enhance T cell activation in situ and improve tumor regression by infiltrating T cells.