AUTOIMMUNITY AND THE IMMUNOTHERAPY OF CANCER: IS THE INDUCTION OF AUTOIMMUNITY A DESIRABLE STRATEGY IN CANCER IMMUNOTHERAPY?

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Genes encoding antigens expressed by tumor cells that could potentially be mployed in recombinant and synthetic anti-cancer vaccines can be grouped into three categories. The first is non-germline genes (encoding sequences that are not part of the "self" repertoire). Examples of such genes include point mutations (mutant Ras, P53), fusion products (Bcr-abl) and viral antigens (E6 and E7). The second category includes germline genes encoding sequences that are not normally expressed in adult tissues. Examples here are genes that are turned on exclusively during developement that are also expressed by tumor cells as well as products of human endogenous retroviruses (HERV). The third catogory is that of germline genes encoding sequences that are expressed in particular tissue and tumor histologies. Examples of these include overexpressed "normal" housekeeping genes, and tissue differentiation Ags.

The three categories of potential tumor antigens are arranged in the order of decreasing tumor specificity and increasing central and peripheral tolerance. Thus, tissue differentiation antigens are not tumor specific since they are expressed by normal tissues as well as tumor cells, and issues of central and peripheral tolerance are likely to bedevil the immunotherapist that attempts to use them as targets for immune responses.

In this light, tissue differentiation antigens are the least attractive category of those listed above. And yet, in the case of melanoma, we are proposing to use melanocyte differentiation antigens (such as MART-1, gp100, Tyrosinase, TRP-1, TRP-2 that are expressed by normal melanocytes and by melanoma cells) as the best targets available for anti-tumor immunotherapies based on recombinant and synthetic vaccines. On the face of it, this seems like a very poor strategy.

There are five major elements that comprise the rationale for this apparently counterintuitive decision: Melanocyte differentiation antigens comprise the majority of the antigens that are recognized by anti-tumor T lymphocytes that are capable of mediating regressions of metastatic melanoma upon adoptive transfer to tumor bearing patients.

Vitiligo is associated with cancer regression in patients undergoing immunotherapy with interleukin-2. In a prospective study of melanoma patients treated with IL-2, none of the 27 nonresponding patients developed vitiligo. Vitiligo was seen 11/43 (26 %) patients who experienced an objective response to treatment. Presumably, vitiligo in the responders results from the autoimmune destruction of normal melanocytes together with the growing tumor. Since no other autoimmune manifestations were observed, the most likely targets of these immune responses were melanocyte differentiation antigens.

The problem of immune tolerance may be surmountable. Patients are obviously not tolerant to all of the epitopes within a given protein. Indeed, tolerance may be relevant for only the most highly presented epitopes.

The problem of lack of tumor specificity may have acceptable consequences ie the destruction of normal tissue may be preferable to a metastatic malignancy.

The strategy of targeting tissue differentiation antigens has application to other malignancies arising from non-essential organs including but not limited to prostate, ovarian and breast cancers.

Our current research efforts include the insertion of the genes encoding tumor rejection antigens into a number of different recombinant viruses including vaccinia viruses, fowlpox viruses, influenza A viruses and adenoviruses. We have also constructed plasmids for naked DNA studies and for studies involving the gene gun. We have taken this approach because we have been encouraged by the observation that many attenuated, killed or recombinant viruses or viral extracts can elicit powerful, specific and life-long immunity (eg. smallpox, rabies, polio and hepatitis). Furthermore, insertion of genes encoding antigens such as B-galactosidase from *Escherichia coli*, chicken ovalbumin (OVA), and nucleoprotein from Vesicular Stomatitis Virus (VSV) into experimental tumor cells elicits very weak, if measurable, cellular immune responses against antigens. In contrast, expression of these same experimental antigens by any number of different recombinant viruses elicits powerful and specific cell-mediated immune reactivities when measured in proliferation, cytokine release and microcytotoxicity assays. Finally and most importantly, mice bearing model-Ag expressing tumors can be treated successfully when they are inoculated with viruses capable of mediating the expression of the same model antigens.

We have just completed the cloning of the murine homologues to MART-1/Melan-A, gp100, tyrosinase, TRP-1 and TRP-2 into a number of recombinant vectors and we will employ the experimental murine tumor B16 to conduct mouse experiments that

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