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Short Communication
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New Strategy for the Identification of Tumor-Associated Antigens that Induce Therapeutic Immune Responses in Tumor-Bearing Mice

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This short report describes a unique strategy designed to identify dominant tumor antigens associated with lung cancer cells with general applicability to other histologic types of cancer. Immunity to dominant tumor antigens can induce therapeutic immune responses in tumor-bearing mice, and patients. In a squamous carcinoma mouse model of non-small cell lung cancer, the antigen-discovery strategy we describe is based on the finding that genes encoding Dominant Tumor-Associated Antigens (TAA) (immunity to dominant tumor antigens formed by proliferating squamous carcinoma cells can lead to tumor regression) are expressed in a highly immunogenic form by a nonmalignant, allogeneic fibroblast cell line transfected with a cDNA expression library from lung cancer cells. The transfected cells, which express the products of multiple genes specifying an array of antigenic determinants, including genes specifying dominant tumor antigens, were selected for antigen discovery. However, as only a small proportion of the transfected cell population was expected to have incorporated gene-segments that specified TAA (the vast majority specified normal cellular constituents), a unique strategy was developed that resulted in the identification of Cyp2e1, a derivative of cytochrome p450, as an immune dominant tumor antigen in murine squamous carcinoma cells and growth factor receptor bound protein 10 (GRB10) as an immune dominant tumor antigen in murine breast cancer cells.

The strategy consisted of dividing aliquots of the suspension of transfected cells into 10-15 small pools (initial inoculums 10E3, a 96 well cell culture plate was used for this purpose, allowing the cells from each pool to increase in number (to approximately 10E7) and then dividing the transfected cell-populations from each pool into two portions. One portion was maintained frozen/viable for later recovery. The remaining portion was co incubated with (mitomycin C-treated) squamous carcinoma cells. Two independent assays, (ELISPOT interferon gamma-release and 51-Cr release cytotoxicity) were used to identify pools that stimulated immunity to the squamous carcinoma cells to the greatest, (and for later use and as a control) to the least extent. Frozen cells from these pools were reestablished in culture, the cell-numbers were expanded and subdivided for additional rounds of immune selection. (Ifthe starting inoculums were sufficiently small, then randomly, some pools would be expected to contain greater numbers of cells that induced the antitumor immune response, i.e., expressed dominant tumor antigens, than others.) After further rounds of immune selection, microarray was used to identify the products of genes over-represented in the cell pool that stimulated the antitumor immune response to the greatest and (for use as a control) to the least extent. Cyp2e1, a derivative to cytochrome p40 was identified as a dominant tumor antigen. As final confirmation of the immunotherapeutic properties of the identified gene-product, a vaccine was prepared by transfer of an expression vector specifying the candidate gene into an allogeneic cell line followed by immunization of mice with squamous cell cancer. The potential immunotherapeutic properties of the identified gene-product were tested in tumor-bearing mice with squamous carcinoma. An analogous strategy was used to identify dominant antigens expressed by breast cancer cells. Using a similar approach, growth factor receptor bound protein 10 (GRB10) was identified as a dominant tumor antigen expressed by breast cancer cells,

Among other advantages of this approach is that as the transferred DNA from the tumor is expressed, the vaccine could be prepared from unusually small amounts of tumor tissue. Patients at an early stage of the disease, when the tumor burden is still small and who are most amenable to immune-based therapy, can receive personalized treatment.

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