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New strategy for the identification of tumor-associated antigens that induce therapeutic immune responses in tumor-bearing mice

Here, author describes a unique strategy designed to identify dominant tumor antigens associated with lung cancer cells. Vaccines that induced 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 described is based on the finding that genes encoding dominant tumor-associated antigens (TAA) (immunity to dominant tumor antigens 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 and Trop1 as immune dominant tumor antigens 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, using a 96 well cell culture plate was used for this purpose, allowing the cells from each pool to increase in number (to approximately 10E7,) small starting inoculums increase the likelihood that some pools will contain greater numbers of cells that express dominant cancer antigens than others). Afterwards the transfected cell-population from each pool was divided 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. We reasoned that if the starting inoculums were sufficiently small, then randomly, some pools would contain greater numbers of cells that induced the antitumor immune response 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.



Figure1: Strategy for enrichment of a cellular cancer vaccine using immunotherapeutic cells A cDNA expression library from SB5b cells, a breast cancer cell line, was transfected into LM fibroblasts. The transfected cell population (10³) was divided into a number of small pools. Cells in the individual pools were allowed to increase in number to approximately 10⁷, by transfer to progressively larger cell culture flasks. Afterward, half of the cells from the individual pools was maintained (frozen/viable) for later recovery. The remaining half was used to immunize C3H/He mice, which were highly susceptible to the growth of the breast cancer cells. Analyzing spleen cells from the immunized mice by two independent means identified pools containing greater numbers of cells that expressed tumor antigens. Highly immunogenic pools were identified and subjected to multiple rounds of enrichment.

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Biography

Cohen completed his medical studies at Washington University (St Louis). Postdoctoral studies were at the University of Chicago, the NIH and the University of Colorado. He has been a member of the faculty of Rutgers University, the University of Chicago and, most recently, the University of Illinois. Cohen has published more than 135 peer-reviewed papers, in the field of tumor immunology, numerous reviews and book chapters. Currently, Cohen is the CEO of Immune Cell Therapy, Inc., a tumor vaccine company.

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