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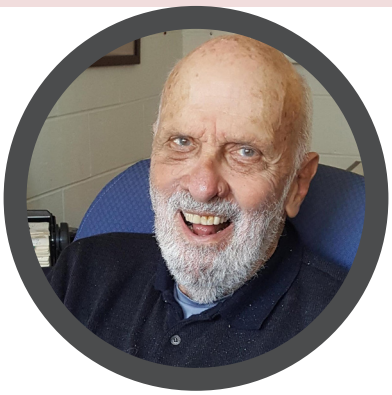
NEW STRATEGY FOR THE IDENTIFICATION OF TUMOR-ASSOCIATED ANTIGENS THAT INDUCE THERAPEUTIC IMMUNE RESPONSES IN TUMOR-BEARING MICE



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We describe a unique strategy designed to identify dominant tumour antigens. The antigen-discovery strategy is based on the finding that genes encoding dominant tumour antigens (TAA) are expressed in a highly immunogenic form by an allogeneic fibroblast cell line transfected with DNA from cancer cells. As the transfected cells, express the products of multiple genes specifying an array of tumour antigens, cells expressing genes specifying dominant tumor antigens that induced therapeutic immune responses were identified for antigen discovery. As only a small proportion of the transfected cell population was expected to have incorporated gene-segments that specified TAA, a unique strategy was developed that resulted in the identification of Cyp2e1, a derivative of cytochrome p450, as an immune dominant tumor antigen in lung cancer cells and growth factor receptor bound protein 10 (GRB10) as an immune dominant tumor antigen in breast cancer cells. The strategy consisted of dividing aliquots of the suspension of transfected cells into 10-15 small pools (initial inoculums 10E3) 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. The cells in the pool that induced immunity to lung cancer to the greatest (and as a control) to the least extent were maintained frozen/viable for later recovery. The remaining portion was co incubated with (mitomycin C-treated) lung cancer cells. ELISPOT interferon gamma-release and 51Cr release cytotoxicity were used to identify pools that stimulated immunity to the lung cancer cells to the greatest and least extent. Frozen cells from these pools were reestablished in culture; the cell-numbers were expanded and subdivided for additional rounds of positive or negative selection. After further rounds, microarray was used to identify the products of genes over-represented in the cell pool that stimulated the antitumor immune response to the greatest extent. Cyp2e1, a derivative of cytochrome p450, was identified as a dominant lung cancer antigen. As final confirmation of the immunotherapeutic properties of the identified gene-product, a vaccine was prepared by transfer of an expression vector specifying Cyp2e1 into an allogeneic cell line followed by immunization of mice with squamous cell lung cancer. An analogous strategy was used to identify dominant antigens expressed by breast cancer cells. Growth factor receptor bound protein 10 (GRB10) was identified as a dominant tumour antigen expressed by breast cancer cells.

Biography

Edward P. Cohen, M.D. is a graduate of Washington University School of Medicine. He did his postgraduate education at the National Institutes of Health, The University of Chicago and the University of Colorado. He is the author of more than 150 peer review publications involving the formation of cellular cancer vaccines. His land mark paper with Jerrold Schwaber was the first to describe the technique used to form monoclonal antibodies. Below is an example of my paper. Schwaber J and Cohen EP 1974 33. Pattern of Immunoglobulin Synthesis and Assembly in a Human-Mouse Somatic Cell Hybrid Clone Somatic Cell Hybrid Clone Proceedings of the National Academy of Sciences of the United States of America. Vol. 71, No. 6 (Jun., 1974), pp. 2203-2207.

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