EDITORIAL

Growth Factor Receptor Monoclonal Antibodies and Cancer Immunotherapy

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With the description of the hybridoma technique by Kohler and Milstein (1), it became apparent that monoclonal antibodies were novel reagents with potential applications in the diagnosis and treatment of malignant diseases. It was hoped that the antigenic specificity intrinsic to these new immunological reagents could be translated into methods of attacking cancers with a degree of specificity not attainable by other modes of treatment. These hopes have remained largely unfulfilled owing to the great difficulty in identifying tumor-specific target antigens (2).

However, despite the lack of absolute targeting specificity, advances have been made in the use of monoclonal antibodies as vehicles to deliver toxins, drugs, and radioisotopes to malignant cells. Clinical trials with monoclonal antibodies to tumor-associated antigens are under way (3). Malignancies of B and T cells are exceptions in that these cells produce unique antigens that are essential components of normal humoral and cellular immune responses. Thus, the idiotypes of surface immunoglobulins and the variable regions of T-cell receptors are highly specific antigenic determinants on malignant lymphocytes, which can be exploited as targets for monoclonal antibodies. In perhaps the most impressive use of monoclonal antibodies to treat a human malignancy, a patient with a B-cell lymphoma went into complete clinical remission for 6 years following anti-idiotypic antibody therapy (4).

In a similar vein, cell-surface receptors for hormones and growth factors are attractive alternatives to tumor-specific antigens as targets for monoclonal antibodies. The potential usefulness of monoclonal antibodies to receptor molecules in preventing or inhibiting the growth of cancer cells has received support from several converging lines of research.

Studies on the growth requirements of cells in serum-free cultures have shown that individual cell types proliferate in response to different sets of growth factors and hormones (5,6). This knowledge suggests that cell proliferation could be impeded by receptor monoclonal antibodies in a relatively cell-type-specific manner through the judicious selection of target receptors. Furthermore, studies of viral oncogenes have demonstrated homologies between oncogene products and growth factors (7,8) or growth-factor receptors (9-12), thus emphasizing the importance of growth-factor action in pathological cell proliferation.

In addition, an increasing number of reports in the literature describe the production by tumor cells of autocrine growth factors and angiogenic factors, which very likely contribute to the formation and growth of tumors in vivo. Together, these lines of investigation provide a rational basis for exploring the vulnerability of cancer cells to monoclonal antibodies directed toward cell-surface receptor molecules.

The receptor for epidermal growth factor (EGF) is but one receptor under study as a potential target antigen for immunotherapy based on monoclonal antibodies. This M, 170,000 plasma-membrane glycoprotein binds both EGF and TGFα through its extracellular domain, and it mediates the growth-stimulating activity of EGF on a variety of cells (13,14). EGF receptors are overexpressed in squamous cell carcinomas (15) and non-neuronal brain tumors (16), and the expression of EGF receptors has been correlated with malignancy in melanomas (17), breast cancers (18), and gastric carcinomas (19).

Five monoclonal antibodies raised against human EGF receptors have been characterized as inhibiting the growth of at least one human tumor cell line in culture (20-24). The mechanism by which tumor cell growth was inhibited in vitro is unknown, but it may have been related to the overexpression of EGF receptors by the target cells or to the interruption of an autocrine mechanism of cell-growth stimulation. Five monoclonal antibodies to human EGF receptors also inhibited the growth of some human tumor xenografts in athymic BALB/c mice (23,25,26). The tumoricidal effects of these antibodies most likely involved host cellular immune responses, and they were mediated, at least in part, by activated macrophages (23,27).

The following general conclusions can be drawn from these studies: Unmodified monoclonal antibodies to EGF receptors can inhibit the growth of tumor cells in vitro and in vivo; antibody-directed inhibition of tumor cell growth in vivo may involve host effector cells; the efficiency with which receptor antibodies inhibit tumor cell growth may depend on their antigenic specificities, their binding affinities, and their class or isotype; individual EGF-receptor monoclonal antibodies do not inhibit the growth of all tumors that have EGF receptors; and not all receptor-bearing tumor cells are subject to antibody-mediated growth inhibition.

An additional clinical application of these antibody reagents, which is currently under examination in experimental animals, is the radioimaging of tumors (28,29). As discussed by Goldenberg et al. in this issue of the Journal, this procedure may be most effective with tumor cells that overexpress target receptor antigens.

Thus, progress is being made in evaluating the suitability of monoclonal antibodies to EGF receptor and to other re-
receptors species (3) as therapeutic reagents. However, much remains to be learned. Hopefully, it will be possible in the future to predict from first principles the therapeutic potential of any given receptor monoclonal antibody. Clinical trials with these reagents will be essential to study toxicity and side effects, to optimize the method and schedule of delivery, and, ultimately, to determine the clinical relevance of receptor monoclonal antibodies.

References

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