

Monoclonal Antibodies in Clinical Immunobiology

Derivation, Potential, and Limitations

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Vertebrate organisms react against an antigen by generating several thousand different immunoglobulin molecules against the antigen. Serum from such organisms therefore contains a multitude of different immunoglobulin molecules with different affinities and avidities. These heterologous sera from hyperimmunized animals or human beings have for several decades been the conventional source of reagents in serology and other types of biological assays based on antibodies. The content of immunoglobulin molecules in the serum of hyperimmunized animals undergoes continuous changes with time. Batches of serum from the same individual taken at different times are therefore not identical in antibody composition and can accordingly not be assumed to have exactly similar reactivity patterns. In addition, the amount of a given conventional anti-serum (antibody) is limited, and this has to some extent hampered the use of antibody-based assays in biology and clinical medicine.

The hybridoma technology for production of monoclonal antibodies (Mabs) (8, 10) circumvents many of the constraints associated with conventional antibodies and consequently broadens the areas of application of antibodies in both basic and clinical research. However, the use of Mabs has pitfalls and limitations that are important to remember, as Mabs are slowly replacing conventional antibodies in a number of different assay systems. The present review

aims to describe the potential usefulness of Mabs in clinical immunobiology, the inherent limitations of the current hybridoma technology, and the improvements that can be foreseen within the next few years. It also describes a number of results already obtained by analysis of immunological disorders with Mabs and the perspectives for application of a broader panel of Mabs in such diseases.

Hybridoma technology

B-lymphocytes and in particular their differentiation products (plasmocytes) produce and secrete antibodies. Each B-lymphocyte secretes only one type of immunoglobulin molecule and the Ig-products secreted from lymphocytes descending from one B-lymphocyte are consequently all secreting the same immunoglobulin molecule. Monoclonal cultures of such cells will accordingly result in supernatants that contain only one single type of immunoglobulin molecule. However, lymphoid cells can only be kept in culture for a very short time and cannot be propagated *in vitro*, although some recent reports have indicated that long-term B-lymphocyte cultures can now be established with a reproducible frequency.

Permanent *in vitro* lines of myeloma cell cultures have been established from several species, including mouse, rat, and human beings. Most of these lines secrete immunoglobulin, but not

of known specificity. *In vitro* experiments demonstrated in the early sixties that spontaneous somatic hybridization may occur between individual cells. Reproducible methods were subsequently established to induce somatic hybridization of cells, and these techniques have been used extensively for gene mapping and for studies of gene expression and differentiation (18). Experiments in the early seventies with hybrids of different myeloma cells with different Ig-product secretion showed that such hybrids can produce the Ig-products of both myeloma cell types. All these experiments, together with the development of tissue culture medium by which hybrids can be promoted selectively in their growth as compared to non-fused cells, were

essential for the development of the monoclonal hybridoma antibody technique (3, 4).

The general procedure for derivation of monoclonal antibodies is schematically outlined in Fig. 1. Mice (usually 3–5) are immunized with the antigen against which Mabs are desired. The antigen preparation does not have to be pure, and, in fact, in some instances it may be advantageous to use impure antigen preparations. The splenic mononuclear cells from the immunized mice are fused in polyethylene glycol with myeloma cells that are growing as permanent lines in culture. However, the myeloma cells must also have a genetic deficiency, which does not allow them to grow under certain conditions. The most commonly used mutants

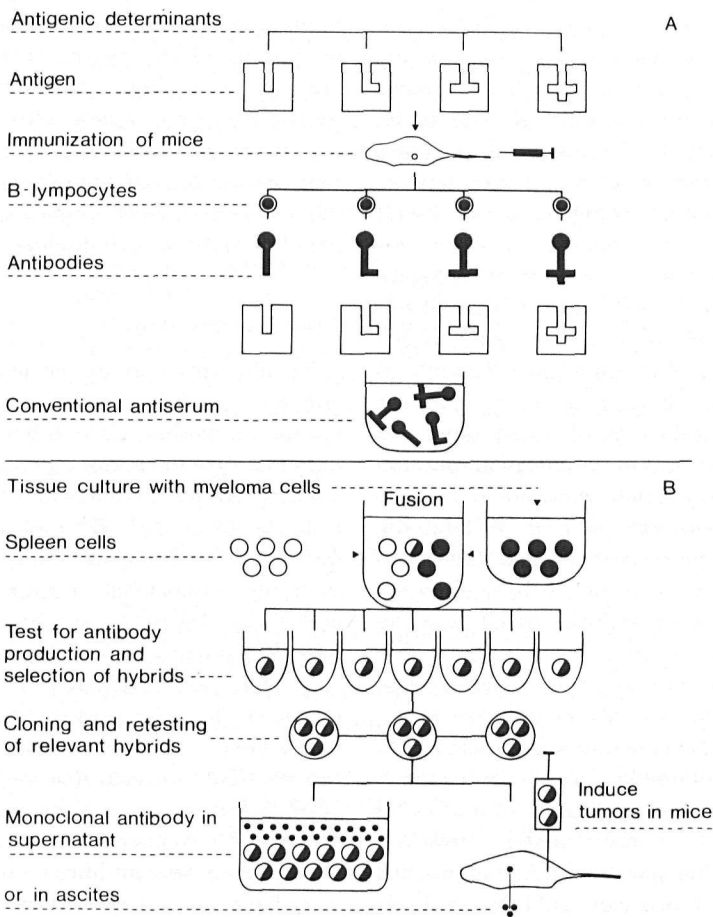


Fig. 1. Difference between derivation of conventional, heterologous antibodies (A) and monoclonal antibodies (B).

lack the enzymes hypoxanthine guanine phosphoribosyl transferase (HPRT) or thymidine kinase (TK), and these cells are consequently unable to incorporate externally supplied hypoxanthine or thymidine. Blockage of the endogenous synthesis of DNA precursors with aminopterin results therefore in death of the cells, even when hypoxanthine and thymidine are supplied in the HAT medium. The mononuclear spleen cells contain the wild salvage pathway enzymes including HPRT and TK, and hybrids between myeloma cells and lymphocytes consequently contain all the enzymes that are needed to grow in a medium containing hypoxanthine, aminopterin, and thymidine. The non-fused mononuclear spleen cells die out eventually because they cannot be propagated *in vitro*.

Polyethylene glycol mediates fusion of the cell membranes of lymphocyte and myeloma, and the cell products immediately after fusion are thus bi- and multinucleated cells. However, a functional hybridoma cell is a mononuclear cell and a spontaneous assembly of the chromosomal material of the two cells into one nucleus is therefore required. This fact has been somewhat ignored despite its close association with some of the other technical aspects of hybridoma technology and has been shown to be of major importance particularly in derivation of human-human hybrids (see below). Spontaneous fusion of the two nuclei requires that they enter mitosis almost simultaneously.

The lymphocyte fusion partner must therefore be in a stage of differentiation with active proliferation. Fusion of mature antibody-secreting plasma cells with myeloma cells will therefore normally not result in proliferative, functional hybrids. The murine mononuclear spleen cells must therefore be harvested in a very narrow time interval after antigen boosting (3–4 days) because the antigen-primed cells are otherwise in a stage of differentiation that does not permit generation of functional hybridoma cells.

The fusion of lymphocytes and myeloma cells is normally done with a lymphocyte:myeloma cell ratio of 5–10:1, typically 10^8 mononuclear spleen cells with $1\text{--}2 \times 10^7$ myeloma cells. The

cells are seeded after fusion in 96-well microtiter plates, and the conventional culture medium is exchanged 24 h later with the selective HAT-medium in which the cells are cultured for 10–14 days. After this period, only hybridoma cells (HPRT+ cells) are growing, and culture supernatants can normally be tested for content of antibody 14–30 days after fusion.

It is of crucial importance that the assay system is fast and reliable, otherwise relevant hybridoma clones risk being overgrown by non-producer clones. Typically, radioimmunoassays or enzyme-linked immunosorbent assays (ELISA) are used for defined antigens, but the data obtained with Mabs against cell surface antigens may vary considerably from assay to assay. We have generated a number of Mabs against cell surface antigens on normal and malignant cells (6, 16). The screening systems were: a) ELISA for Ig-production; b) cell-binding ELISA; c) fluorescence-activated cell sorter (FACS) analysis; d) microcytotoxicity. The results could differ significantly between the individual test systems, particularly production and cell surface specificity, which probably reflects the significant variability of the individual antibody in its affinity to plastic and to its specific antigen, respectively. In routine screening procedures for cell surface antigens, two of the four assays must be positive in order to continue work with a given hybridoma clone.

Hybridomas that secrete Ig with desired specificity are cloned either by limiting dilution, or in semisolid culture medium (agar; agarose; methyl-cellulose). The cloned hybridomas can then be expanded either in mice or in large cultures, and the Mab purified from ascites or culture supernatants.

Human-human Mabs

Diagnostic and therapeutical maneuvers with Mabs in human beings should preferably be done with human immunoglobulins, and their clinical potential has been reviewed elsewhere (7). Limited clinical trials with murine Mabs indicate that almost all patients generate anti-mouse Ig antibodies, except for a few patients who due to their disease probably had a very

compromised immune system. It is conceivable that human Mabs are better tolerated on injection into human beings, although anti-idiotypic responses cannot be excluded as a complicating factor.

We developed the human-human hybridoma technology for another reason. Individual malignant neoplasms consist of tumor cells with variable phenotypic features, and this intra-tumoral phenotypic diversity (IPD) has profound cancer biological importance (16). IPD is also expressed at the level of cell surface antigens of the malignant cells, and it could be expected that antigenic heterogeneity, at least in part, could be elucidated by murine Mabs. However, such Mabs do not indicate whether any of the antigenic components are immunogenic in the tumor-bearing individual. This is important to investigate as it has been debated for years whether malignant neoplasms elicit an immune response in the autologous host. However, it has not been technically possible to analyse the anti-tumor reactivity of Ig-products from B-lymphocytes of the tumor-bearing human beings. Immobilization of B-lymphocytes by human hybridoma technology makes such studies possible and was also our reason for developing this technology (14), and it is possible that the human hybridoma technique enables a very refined dissection of the human B-lymphocyte response to antigens encoded by human gene products.

In the last few years several human lines have been shown useful as malignant fusion partners, but all have a significantly reduced hybrid yield compared with the various rodent hybridoma systems. Derivation of the appropriate mouse myeloma cell lines required many years of tissue culturing, and it is possible that optimal human myeloma cell lines have not yet been developed, and that this is a contributing factor to the low hybrid yield. However, our experience throughout the last 2½ years with human hybridoma technology (15) has proved the importance of having B-lymphocytes at the stage of differentiation that is optimal for fusion. For obvious reasons human B-lymphocytes cannot be obtained 3–4 days after antigen-boosting as in the mouse system, and other

methods are therefore needed to obtain human B-lymphocytes in the appropriate stage(s) of differentiation. These methods include *in vitro* antigen-priming and use of substances that induce de-differentiation; however, several years of research is required before these procedures are developed to the stage of practical routine application.

A few clinically relevant human monoclonal hybridoma antibodies have, however, already been obtained. B-lymphocytes from acute myeloid leukemia (AML) patients in clinical remission were fused with a human myeloma cell line and an antibody derived that identifies AML cells in a certain subclass (M2) according to the French-American-British (FAB) classification (16, 17). Furthermore, human monoclonal antibodies against leucocytes were obtained by fusion of human myeloma cells with B-lymphocytes from patients with systemic lupus erythematosus who were found to have cytotoxic auto-antibodies against their leucocytes. Both of these examples also demonstrated the possibility of using human hybridoma technology to dissect the spectrum of the B-lymphocyte response in human beings.

Biological properties of monoclonal antibodies

The selective fusion of myeloma cells with B-lymphocytes at a certain stage of differentiation results in a significantly higher percentage of antibody-secreting hybrids (50–80%) than is present among the mononuclear spleen cells from a hyperimmunized animal (about 0.5–1%). A contributing factor to this high amount may be the Ig-secreting apparatus of the myeloma cell and the Ig-expression (but not secretion) of the B-lymphocyte. The selectivity of the fusion process for a certain type of B-lymphocyte cannot be extended to a certain type of quality of Ig-product secreted from hybrids. In other words, the general pattern is that the antibodies secreted from established hybrids represent a cross-section of the antibodies secreted in an immunized organism, but this does not validate a direct comparison between Mabs and corresponding conventional antisera. The composition of the latter depends

on the half-life of the various antibodies *in vivo*, which again is associated with the stage of differentiation of the Ig-secreting B-lymphocyte.

Most Mabs derived by hybridoma technology have avidities far below the corresponding conventional antisera. The reason for this is more or less implicit in the technical comments already given above. Antibodies with high avidity comprise about 1–3% of the total amounts of antibodies in a conventional antisera. With an equal percent distribution of different Ig-secreting B-lymphocytes, it is to be expected that most of the hybrids are secreting Mabs with low avidity. If high avidity Mabs are of particular importance, the screening assays must be designed to exclude low avidity antibodies.

The practical problems with the use of low avidity antibodies are associated with one of the most frequently occurring mistakes in the interpretation of results obtained with Mabs. The specificity of an antibody is a quantitative phenomenon that is determined by its avidity to a defined antigenic structure as compared to other irrelevant antigens (11). The specificity of a given Ig-molecule is therefore not increased because it is completely purified, as when it is part of an antiserum. The monoclonal derivation of an antibody sample therefore does not exclude non-specific cross-reactivity. In fact, use of low avidity antibodies may reduce the difference between the amount of Ig-molecules bound to a specific determinant, as compared to non-specific binding, to a degree that confuses interpretation of the results. Binding of several different antibodies to different determinants on the same molecule may be an important natural amplification system to increase the difference between the antigen-specific binding and the non-specific binding. For example: Given an antigen with 10 determinants. A monoclonal antibody is derived that binds to nine antigenic determinants per one irrelevant determinant. If 10 different Mabs, binding to each of the 10 determinants of the antigen, were available with the same ratio 9:1 for specific versus non-specific binding and each antibody bound to different irrelevant determinants, the numeric difference between an-

tigen-specific bound immunoglobulin molecules would be 80 instead of 8, i.e. a 10 times amplification.

These considerations are of importance when comparing Mabs with conventional antisera. A high avidity conventional antiserum will in most cases be more useful than a low avidity Mab. It is possible that mixtures of Mabs can circumvent these obstacles in the use of a single Mab preparation, as illustrated by our own work in cancer biology (6, 16). It should also be remembered that lack of reactivity with a Mab does not prove lack of antigenic determinant, as minor environmental-induced changes of the antigenic determinant may alter antibody reactivity.

Mabs do have some biological properties that at first sight may appear odd to the investigator who is used to conventional antisera. It is thus not surprising that binding of a bivalent antibody to a monovalent antigen does not result in a precipitation reaction. Also, whereas conventional antisera react in a comparable way to experimental procedures such as freezing, freeze-drying, and iodination, Mabs react very variably. The reason lies in the heterogeneous composition of conventional sera, so that loss of 50% of the molecules will only result in a slight titer change, whereas in the case of a Mab sensitive to a given procedure, it will result in complete loss of antibody activity. General guidelines for the handling of Mabs can therefore not be directly deduced from the procedures already employed in relation to conventional antisera.

SOME CLINICAL APPLICATIONS

Mabs will probably replace conventional antisera in a number of assays that are currently based on the use of heterologous antibodies. Furthermore, it is conceivable that Mabs will be instrumental in dissection of cellular functions and their orchestration – or lack of such resulting in clinically manifested diseases (12). In this context, the aspects in relation to immunoregulatory disorders, organ and tissue transplantation, and malignant neoplastic diseases will be discussed.

Immunoregulatory disorders

Mabs are now available for identification of subsets of lymphoid cells such as the pan T-lymphocyte pool, suppressor/killer T-lymphocytes, helper T-lymphocytes, and B-lymphocytes. In addition, Mabs with high specificity for monocytes have recently become available, and supplement the anti-lymphocyte Mabs, so that the various known components of the immune system can now be enumerated in great detail. Here it should be remembered that alteration in the *number* of the different subsets of immunocompetent cells does not necessarily reflect a functional disturbance in the immune system. A high amount of T-suppressor/killer cells is not invariably associated with immunosuppression or high cytotoxic cell activity. In other words, the data obtained with Mabs are static parameters, and functional aspects cannot directly be deduced.

Patients with inactive rheumatic arthritis have T-cell subset levels indistinguishable from healthy persons, whereas patients with active disease seem to have elevated T-helper and decreased T-suppressor cell numbers. It is tempting to speculate that the low T-cell suppressor level results in abnormal aggressive lymphocyte activity, but with the currently available methods this remains a speculation.

About 10–20% of patients with systemic lupus erythematosus (SLE) have autoantibodies against their own T-cells, and, as reported in some studies, particularly against the T-suppressor cell compartment. The group of SLE patients with autoantibodies however, is a part of the total amount of SLE-patients and may not reflect the dominant immunodysregulatory pattern in SLE. Recent experiments suggest that the impaired suppression may reflect impaired functions in the immunoregulatory circuits rather than a simple decrease in suppressor T-cells as a result of lysis through cytotoxic autoantibodies. SLE is also an example of a disease where human-human hybridoma technology can be used to dissect the pattern of autoimmune reactivity at the B-lymphocyte level and has already been used in this type of analyses (2, 19).

Sjögren's syndrome is, among other features, characterized by lymphoid infiltration of exocrine glands and by circulating autoantibodies. Analyses of peripheral blood lymphocytes have demonstrated a marked increase in helper T-lymphocytes and a decrease in suppressor T-cells. This increase in the helper cell compartment was well correlated with lymphoid infiltration in lip biopsies, but not with specific autoantibodies or rheumatic factors. It is thus quite possible that the increased helper T-cell ratio is associated with, but not causing, the generation of autoantibodies.

Some patients with active atopic dermatitis have a selective reduction in T-suppressor/helper lymphocytes, whereas patients with respiratory allergic disease have normal ratios in the various lymphocyte subsets. A recent study has indicated increased T-helper/T-suppressor/killer ratio in patients with hayfever.

Multiple sclerosis and myasthenia gravis are both diseases that are suspected to have im-

Table 1
Alterations in T-lymphocyte subsets in various immunoregulatory disorders

Disease	Pan-T	T-Helper	T-sup- pressor/ killer	Helper: suppressor/ killer ratio
Active rheumatic arthritis	↓	→	↓	↑
Systemic lupus erythematosus*	→	→	(↑?) →	→
Sjögren's syndrome	(↑) →	↑	↓	↑
Multiple sclerosis	→	→	↓	↑
Myasthenia gravis	→	↑	↓	↑
Atopic dermatitis	↓	→	↓	↑

* Only patients without anti-T-lymphocyte autoantibodies. The patients with autoantibodies have reduced suppressor T-cell numbers.

munoloigcal functions as a major etiological cause. In both of these diseases, a reduced amount of suppressor/killer T-cells was found during active phases of the disease, whereas normal levels in T-cell subsets were generally found in periods with inactive disease. The same pattern of variations in T-cell subsets has been found in other types of immunologically related diseases like pemphigus vulgaris, membranous glomerulonephritis, and hemolytic anemia. Also ageing is associated with altered T-lymphocyte subset proportions, again with a decrease in suppressor/killer T-lymphocytes and thus a relative increase in cells with T-helper phenotype.

All the investigations referred to above (summarized in Table 1) have been performed with Mabs, that various *in vitro* assays have shown react preferentially with certain functional subsets of lymphocytes, particularly T-lymphocytes; Mabs against these cells became available shortly after the development of hybridoma technology (9, 21). Several recent analyses on the functional activities of the various subsets identified with Mabs have clearly demonstrated an overlap in binding patterns among the different subsets. Mabs are therefore not absolutely specific for a given functional subset of cells, and the functional aspects of numerical changes in a given subset under pathophysiological conditions should therefore be deduced with the greatest caution. The biological consequences of the disturbances in the numbers of T-lymphocyte subsets in the various diseases mentioned above are therefore still unclear.

Mabs in tissue and organ transplantation

The rapid development of Mabs against lymphocyte subsets resulted for obvious reasons in protocols for the clinical application of such antibodies in transplantation, in order to prevent graft rejection and graft-versus-host phenomena that occur as a consequence of undesired lymphocyte activity. These protocols have concentrated on a) treatment of patients *in vivo*, and b) pretreatment of the graft to eliminate undesired cellular elements.

In vivo application of Mabs against a pan-T cell population is based on the fact that graft rejection is caused by T-cell reactivity, and that the currently used immunosuppressive drugs have many undesired side effects. Cytotoxic antibodies with T-lymphocyte specificity should have the potential to selectively reduce or completely eliminate the T-cell mediated graft rejection. This has been the theoretical background for the many clinical trials carried out with heterologous anti-T-lymphocyte globulin (ATG) that was obtained from hyperimmunized horses or other large animals. The immunosuppressive effect of ATG in recipients of organ grafts (primarily kidneys) is debatable and has in the best series only resulted in slight improvements of the results already obtained with more conventional immunosuppressants. ATG has also a number of clinically significant side effects, such as chills and fever, skin erythema, pruritus, and thrombocytopenia. In contrast, toxic effects on other cellular components of the bone marrow are negligible, and it is, in fact, a puzzling observation that ATG may initiate bone marrow proliferation and maturation in patients with aplastic anemia.

Mabs against T-lymphocytes have the potential to circumvent many of the inconveniences of ATG and at the same time exert the same effect on T-lymphocytes. Such Mabs are now commercially available (OTK-series (Ortho) or Leu-series (Becton-Dickinson)). The OKT-4 antibody has been used as immunosuppressive substance in subhuman primates that had received heterotypic renal grafts. A prolonged graft survival was observed in a majority of the animals. Similar results have been obtained with other T-cell antibodies. These results encouraged application of similar anti-T-lymphocyte antibodies (primarily OKT-3) in kidney allograft recipients. Pilot studies indicated that the Mabs were well tolerated and had beneficial effects. However, larger series of experiments have shown that a) rejection episodes recurred after cessation of Mab therapy and b) antibodies against murine immunoglobulins were generated in virtually all patients. The experience from the subhuman primate investigations can only be used to a limited extent in the

human situation. It seems from the presently available data that human anti-T-lymphocyte Mabs may result in an improvement of the rather limited success with murine Mabs in the prevention of kidney graft rejection in human beings, because it is conceivable that the immune reaction against the injected immunoglobulin will be greatly reduced and limited to anti-idiotypic antibodies.

Bone marrow transplantation has become common clinical practice in several immunological and hematological disorders. These transplantations are often complicated by serious infections (e.g. with cytomegalovirus), failure in graft take, and graft-versus-host (GVH) reactions in both acute and chronic forms. Mabs against T-lymphocytes should therefore have the potential of removing the T-lymphocytes from the graft and reducing or completely eliminating GVH reactions. Small series of clinical bone marrow transplantation protocols have investigated this possibility, but the results are inconclusive. The antibodies have been directed against mature T-lymphocytes, and T-lymphocyte precursors are consequently not removed. It is quite possible that also these precursor T-cells must be removed before a beneficial effect can be expected from this type of *in vitro* treatment of the marrow prior to grafting.

A logical extension of these thoughts is the attempt to clean the bone marrow of malignant cells in autologous bone marrow transplantation in patients with lymphoid leukemia. Again, this assumes that the leukemic cells all express the determinant against which the Mab is raised. However, increasing amounts of data strongly indicate that leukemic cell populations are antigenically heterogeneous, and it can consequently not be expected that all leukemia cells will be eliminated. It will probably be necessary to use a panel of Mabs to reach and eliminate all antigenic variants in the leukemic cell population – if at all feasible.

Selection of appropriate donor-recipient combinations in transplantation is based on histocompatibility typing. The antisera are obtained from naturally immunized patients or from conventional animal (e.g. rabbit) anti-

bodies, and lack of sufficient amounts of a specific antibody is often a serious limiting factor. It seems quite possible that Mabs will replace the conventional antisera in tissue typing, and a number of Mabs against monomorphic and polymorphic HLA-determinants have already been reported (1).

Monoclonal antibodies in cancer biology

Monoclonal antibodies have a very broad potential applicability in cancerology (13). It is beyond the scope of this paper to discuss all the areas in tumor biology in which monoclonal antibodies may be useful, as it would require an extensive outline of tumor-biological problems. As mentioned above, we developed the human monoclonal antibody technique in order to use it in studies on the variability in the characteristics of human malignant tumors. This variability has a major impact on experimental studies, diagnosis, and therapy (6). The emerging pattern is that the characteristic features of the cells vary, so that some cells have a high proliferative activity, etc., and it has been possible to identify and isolate such subsets (e.g. cells of high and low metastatic potential) of tumor cells by monoclonal antibodies in experimental tumor systems.

Clinical *in vitro* application of monoclonal antibodies is already being used in the identification of lymphoid tumors (5). Monoclonal antibodies against a given tissue can be used on biopsy material to identify cells of such a tissue in organs where they normally do not occur. If thus a monoclonal antibody specific for prostate cells reacts with cells in inguinal lymph nodes of a patient with prostate cancer, it is highly probable that the cells are metastases from the patient's cancer. Considerable effort is being devoted to the generation of monoclonal antibodies specific for various tissues. Some murine monoclonal antibodies have also been reported to react specifically with tumor cells. However, on careful examination such antibodies have been found also to react with some fetal tissues. This, however, does not disturb the practical use of these antibodies.

More important is the impact of variability in tumor characteristics on the use of tumor-directed antibodies. The variability may imply that some tumor cells may be negative for the antigen against which the antibody reacts and may result in "antigen-negative" metastatic foci that consequently are not revealed by the antibody. Mabs may also induce antigenic modulation and thereby result in antigen-negative tumor cell variants.

Murine monoclonal antibodies against antigens on some experimental tumors have been shown to have an inhibitory effect on tumor growth. Injection of tumor-directed antibody in humans may, therefore, in itself have an antitumoral effect. However, this effect can probably be significantly increased by coupling the antibody to a cytotoxic agent, and a number of investigations are currently being undertaken to study these possibilities. Also a few clinical trials with mouse monoclonal antibodies have been carried out with apparently positive effects. However, the trials are still at a preliminary stage, and it is advisable not to draw too far-reaching conclusions from them. It is beyond doubt that Mabs are very potential tools in both experimental and clinical oncology. However, with the increasing understanding of the complexity of the phenotypic traits of malignant cell population, the results obtained with Mabs have to be interpreted with great caution when applied as a therapeutic and diagnostic reagent.

Epilogue

Monoclonal antibodies as produced by hybridoma technology have a number of advantages compared with conventional antisera. The purity of Mabs, however, does not exclude cross-reactivity, and the low avidity of many Mabs will impose a number of limitations on the use of Mabs as produced by current technology. It is, however, conceivable that future technological improvements will produce Mabs with high avidity and perhaps from cell cultures that are a result of expanded non-malignant human B-lymphocytes. Mabs are already slowly replacing conventional sera in a number

of biological disciplines, including clinical immunology. With a continuation of the current rapid expansion in the field of monoclonal antibody technology it can be expected that Mabs will be an important tool in the daily work of clinical immunologists 5–10 years from now.

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