A Monoclonal Antibody That Precipitates the Glycoprotein Receptor for Epidermal Growth Factor Is Directed against the Human Blood Group H Type 1 Antigen*

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Monoclonal antibody 101 produced by a hybridoma obtained by fusion with NS-1 myeloma cells of spleen cells from a mouse immunized with the human epidermoid carcinoma cell line, A431, specifically precipitates epidermal growth factor receptor, a glycoprotein of 170,000 M, solubilized from A431 cell membranes (Richert, N. D., Willingham, M. C., and Pastan, I. H. (1983) J. Biol. Chem. 258, 8902–8907). The antibody also binds to neutral glycolipids extracted from A431 cells as evidenced by solid phase radioimmunoassay and by autoradiography. Binding of antibody to its target is inhibited by lacto-N-fucopentaose I but not by 2'-fucosyllactose or related oligosaccharides. Thus, antibody 101 is probably directed against the human blood group H type 1 sugar sequence Fucα1-2Galβ1-4GlcNAc... This sequence presumably occurs on the epidermal growth factor receptor. Monoclonal antibody 102 produced by another hybridoma from the same fusion has the same cell specificity as antibody 101 and also binds to neutral glycolipids. However, binding of antibody 102 to its target is inhibited by 2'-fucosyllactose and not by lacto-N-fucopentaose I or related oligosaccharides. Thus, antibody 102 is probably directed against the human blood group H type 2 sugar sequence Fucα1-2Galβ1-4GlcNAc... Antibody 102 does not precipitate solubilized epidermal growth factor receptor. Both antibodies bind to neutral glycolipids extracted from human erythrocytes belonging to blood group O but not to neutral glycolipids extracted from human erythrocytes with the "Bombay" phenotype.

To obtain monoclonal antibodies against the epidermal growth factor receptor, Balb/c mice were immunized with A431 cells, a human epidermoid carcinoma cell line. A431 cells are widely used for studies on EGF receptors because they contain about 2 × 10⁶ receptors/cell (2, 3). After fusion of the mouse spleen cells with NS-1 myeloma cells, a hybridoma was obtained that produces an IgG antibody (antibody 101) which specifically precipitates the solubilized EGF receptor of A431 cells (4). Evidence that antibody 101 recognizes the EGF receptor is as follows. The antibody precipitates a 170 K glycoprotein from metabolically labeled A431 cells; the 170 K protein is phosphorylated when cell cultures or membranes are incubated with EGF; and the antibody specifically precipitates 125I-EGF covalently cross-linked to its receptor. Antibody 101 does not block the binding of EGF nor does it stimulate receptor phosphorylation. Furthermore, the antibody is cell type specific in that it does not recognize the EGF receptors of KB cells, Swiss 3T3 cells, or normal rat fibroblasts. There are about 9 × 10⁶ antibody molecules bound/A431 cell which is 5-fold higher than the number of EGF receptors. This suggests that the antibody recognizes other A431 cell surface determinants in addition to those on the EGF receptor. To explain these findings we proposed that antibody 101 might be directed against the carbohydrate sequence found in EGF receptors from A431 cells and that the additional determinants for the antibody on A431 cells are due to glycolipids containing the same carbohydrate sequence (4). Glycoproteins and glycolipids often have the same carbohydrate antigens (5).

The data presented in this paper demonstrate that antibody 101 is directed against the human blood group H type 1 sugar sequence Fucα1-2Galβ1-4GlcNAc... which occurs in glycolipids as well as in the EGF receptor. A second hybridoma from the same fusion produces an IgM antibody (antibody 102) directed against the human blood group H type 2 sugar sequence Fucα1-2Galβ1-4GlcNAc... Antibody 102 does not precipitate the solubilized EGF receptor of A431 cells.

EXPERIMENTAL PROCEDURES

Materials—2'-Fucosyllactose, 3-fucosyllactose, lacto-N-tetraose, lacto-N-fucopentaose I, and lacto-N-fucopentaose II were isolated from human milk (6). H₂, glycolipid (7), Ose₄Cer (a branched glycolipid containing 10 glycosyl residues), and Ose₅Cer (a branched glycolipid containing 12 glycosyl residues) were kindly supplied by Dr. S. I. Hakomori (Fred Hutchinson Cancer Research Center, Seattle, WA). Other neutral glycolipids were isolated from various tissues (8). For structures see Table I.

Affinity-purified goat antibodies to mouse IgM (μ) and mouse IgG (γ) were purchased from Kirkegaard and Perry Laboratories, Inc. (Gaithersburg, MD) and were iodinated by the Iodo-Gen method (4) to a specific activity of 50 µCi/µg of protein. Rabbit anti-mouse IgG and rhodamine-labeled goat anti-mouse antisera (Cappel Laboratories, Westchester, PA) were affinity-purified on a column of mouse IgG (Cappel Laboratories, Westchester, PA) coupled to cyanoan bromide-activated Sepharose.

Cells—The A431 human epidermoid carcinoma cell line was obtained from Dr. George Todaro (NIH). KB cells were obtained from the American Type Culture Collection (Rockville, MD). Both cell
lines were maintained in Dulbecco's modified Eagle's medium with 10% fetal bovine serum. Human blood group O erythrocytes were obtained from the National Institutes of Health blood bank and "Bombay" erythrocytes from the Central Blood Bank, Pittsburgh, PA. Membranes were prepared from A431 cells grown in 5 roller bottles by the method of Thom et al. (9). The final membrane pellet was stored at -70 °C.

Monoclonal Antibodies—Monoclonal antibodies 101 and 102 were produced by hybridomas resulting from the fusion of NS-1 myeloma cells with spleen cells from a Balb/c mouse immunized with A431 cells. The positive hybrid clones were selected in hypoxanthine, aminopterin, thymidine medium, then cloned twice by limiting dilution on normal Balb/c spleen feeder layers (4). Antibody 101 is an IgG type and antibody 102 is an IgM as determined by incubation with [3]S]methionine (250 μCi/ml) (Amersham, 1000 Ci/mmol) and precipitation of the radiolabeled antibodies with affinity-purified, subclass-specific rabbit anti-mouse serum and Staphylococcus aureus (4). Purified antibodies were obtained by growing the hybrid clones in roller bottles. About 5 liters of supernatant fluid from each were harvested. Antibody 101 was purified by chromatography on protein A Sepharose CL-4B (Pharmacia, Piscataway, NJ) as described (4). Antibody 102 was purified by chromatography on a column of affinity-purified rabbit anti-mouse IgG coupled to cyanogen bromide-activated Sepharose CL-4B (Pharmacia). The purified antibodies were dialyzed against phosphate-buffered saline (NaCl 0.15 M, sodium phosphate, pH 7.4) containing 0.68 mM CaCl₂ and 0.49 mM MgCl₂ (Dulbecco's phosphate-buffered saline; Gibco, Grand Island, NY) and stored at 1-2 mg/ml at -70 °C.

TABLE I

| Carbohydrate | Structure |
|--------------|-----------|
| Lactose      | Galβ1-4Glc |
| Lactose      | Fucα1-2Galβ1-4Glc |
| Lacto-N-tetraose | Galβ1-3GlcNacβ1-3Galβ1-4Glc |
| Lacto-N-fucopentose I | Galβ1-3GlcNacβ1-3Galβ1-4Glc |
| Lacto-N-fucopentose II | Galβ1-3GlcNacβ1-3Galβ1-4Glc |
| Lactosylceramide | Galα1-4Galα1-4Glc-Cer |
| Trihexylceramide | GalNAcβ1-3Galα1-4Galα1-4Glc-Cer |
| Globoside    | Galβ1-4GlcNacβ1-3Galβ1-4Glc |
| Asialo-GM1   | Galβ1-3GlcNacβ1-4Galβ1-4Glc |
| H₂ glycolipid| Fucα1-2Galβ1-4GlcNacβ1-3Galβ1-4GlcNacβ1-3Galβ1-4Glc |

Indirect Immunofluorescence—Live A431 cell cultures plated at a density of 3 x 10⁵ cells/35-mm dish 1 day before use are used for immunofluorescent studies. For incubation with the cell monolayers, antibodies 101 and 102 are diluted to 5 μg/ml and 25 μg/ml, respectively, in Dulbecco's PBS containing 2 mg/ml of bovine serum albumin (Dulbecco's PBS-BSA). Oligosaccharides to be tested are added to the antibody stock solutions to a final concentration of 10 μg/ml (12-20 mM).

The A431 cell cultures are washed twice with ice-cold Dulbecco's PBS-BSA, then incubated with 0.5 ml of each diluted antibody alone or with antibody plus oligosaccharide for 30 min at 4 °C. The monolayers are washed 4 times with ice-cold Dulbecco's PBS-BSA and then incubated with rhodamine-labeled affinity-purified goat anti-mouse IgG (50 μg/ml) in the same buffer. After 30 min at 4 °C, the monolayers are washed 4 times with cold PBS, fixed with 3% formalin in PBS (5 min, 4 °C), and mounted in glycerol under a 25-mm No. 1 coverslip.

Isolation of Glycolipids—Lipids are extracted from A431 and KB cells and from O blood and Bombay blood with chloroform/methanol/water (4:8:3, by volume) as described by Svennerholm and Fredman (10). Neutral and acidic lipids are separated by ion exchange chromatography on DEAE-Sepharose CL-6B in the acetate form. The acidic lipids are extracted from the resin with 10 bed volumes of 0.05 M potassium acetate in methanol and desalted by dialyses. Neutral glycolipids are separated from phospholipids in the neutral fraction by saponification and subsequent silica gel chromatography (8).

Solid Phase Radioimmunoassay—The binding of antibody to glycolipid is measured by solid phase radioimmunoassay at room temperature, as previously described (7). Glycolipid in 20 μl of methanol is added to wells of a round bottom polyvinylchloride microtiter plate (Dynatech, Alexandria, VA) and the solution dried by evaporation. When A431 cell membranes are used as targets, 40 μl of a membrane suspension in PBS (containing 40 μg of membranes for antibody 101 and 3 μg of membranes for antibody 102) are added to the wells. After incubation for 1 h at 37 °C the wells are washed four times with cold PBS. The wells with glycolipid or cell membrane targets are then filled with PBS containing 1% bovine serum albumin (Buffer A). After 30 min, the wells are emptied and to each was added monoclonal antibody diluted with Buffer A to 10 μg/ml (antibody 101) and 50 μg/ml (antibody 102). Twenty μl of antibody solution are added to glycolipid-coated wells and 40 μl to membrane-coated wells. The wells are covered with Parafilm, incubated 3 h, washed four times with PBS, and then to each are added 20 μl of 125I-labeled antisem IgG or IgM from goat in Buffer A (approximately 20,000 cpm). After 6-12 h, the wells are washed six times with cold PBS, cut from the plate, and assayed for 125I in an Auto-Gamma spectrometer.

For hapten inhibition studies the monoclonal antibodies are preincubated for 1 h at room temperature with the various oligosaccharides in Buffer A.

 Autoradiography of Glycolipid Antigens—Glycolipid antigens are detected on thin layer chromatograms by autoradiography as previously described (11). Glycolipids are chromatographed on aluminum-backed high performance thin layer chromatography plates (Silica Gel 60, E. Merek, Darmstadt, West Germany; American supplier, Applied Analytical Services, Wilmington, NC) in chloroform/methanol/0.25% KCl in water (60:40:9, by volume). Reference glycolipids and glycolipids in cell extracts detected by orcinol reagent are chromatographed on the same plate. After air-drying the chromatogram, the part used for chemical staining is cut off and the remaining part soaked for 30 s in a saturated solution of polyisobutylmethacrylate (Polysciences, Inc., Warrington, PA) in hexane. The dried chromatogram is then sprayed with PBS and immediately soaked in Buffer A until the silica gel is wet (about 10 min). The plate is then removed, placed on a Parafilm-coated glass plate in a Petri dish, and overlayed with monoclonal antibody solutions diluted with Buffer A as described above (about 50 μl/cm²) and incubated for 3 h at 4 °C. The chromatogram is washed by dipping in four successive changes of cold PBS at 1-mm intervals, then placed on a new Parafilm-coated glass plate in a Petri dish, and immediately overlayed with Buffer A, approximately 60 μl/cm², containing 10 cpm/ml of 125I-labeled antiserum IgG or IgM antibodies. After 6 h at 4 °C, the chromatogram is washed as before in cold PBS, dried, and exposed to XR5 X-ray film (Eastman-Kodak, Rochester, NY) for 12 h.

RESULTS

Previous experiments using immunofluorescence showed that monoclonal antibody 101 binds to A431 cells but not KB
neutral glycolipids extracted from KB cells (Fig. 1). There is more antigen for antibody 102 in the A431 cell extract than for antibody 101. Maximum binding of antibody 102 is achieved with glycolipids from approximately 0.6 µg of cells whereas binding of antibody 101 is still increasing with glycolipids from approximately 60 µg of cells (Fig. 1). Neither antibody binds to gangliosides extracted from A431 cells or KB cells in solid phase radioimmunoassay (data not shown).

The difference in antigen level of the two antibodies in glycolipid extracts can also be demonstrated by autoradiography (Fig. 2). By this procedure, antibody 101 barely detects antigens in glycolipids from 0.1 mg of A431 cells (lane 1) in contrast to antibody 102 (lane 5). In addition, it is clear from a comparison of lane 3 with lane 5 that the two antibodies detect different antigens. Neither antibody detects antigens in glycolipids from KB cells (lanes 2, 4, and 6). Both antibodies detect antigens in glycolipids from blood group O erythrocytes (lanes 9, 11, and 13). Again, there is much more antigen for antibody 102 than for antibody 101 in these glycolipids. Neither antibody detects antigens in glycolipids from Bombay erythrocytes (lanes 10, 12, and 14), suggesting that both are directed against the human blood group H antigen which is missing in the Bombay phenotype (5). The large diffuse spots as opposed to bands seen in lanes 4, 9, 10, and 14 represent nonspecific binding of antibody to lipid material and often occur when large quantities of extracts are chromatographed. The antigens from A431 cells detected by the antibodies are minor glycolipids as none of them are visualized with orcinol reagent (lane 15). The antigens de-

Fig. 1. Binding of antibody 101 and 102 to neutral glycolipids from A431 and KB cells. Solid phase radioimmunoassays were performed under “Experimental Procedures.” Binding to neutral glycolipids from A431 cells (○○○) and to neutral glycolipids from KB cells (O--O○○).
Antibodies were added in the absence of the following oligosaccharides: 20 mM 2'-fucosyllactose (2'FL) (I), and fucopentaose I (LNFI) (D). Binding of antibody 101 to A431 cells in the absence of oligosaccharides is shown in Fig. 4A and B. Binding of antibody 101 to A431 cells is completely inhibited by 12 mM lacto-N-fucopentaose I (Fig. 4G). Binding of antibody 101 is not inhibited by 20 mM 2'-fucosyllactose (Fig. 4C), 20 mM 3-fucosyllactose (Fig. 4E), or 12 mM lacto-N-fucopentaose II (Fig. 4F). In contrast, binding of antibody 102 is completely inhibited by 20 mM 2'-fucosyllactose (Fig. 4D). Binding of antibody 102 is not inhibited by 20 mM 3-fucosyllactose (Fig. 4F), 12 mM lacto-N-fucopentaose I (Fig. 4H), or 12 mM lacto-N-fucopentaose II (Fig. 4I).

The specificity of antibody 102 for the H type 2 sugar sequence was also confirmed using H2 glycolipid which contains this sequence (Table I). In solid phase radioimmunoassay, antibody 102 binds to H2 glycolipid but not to globoside (Fig. 5). Half-maximal binding is obtained with approximately 3 pmol of H2 glycolipid which is in the same range as results obtained with monoclonal antibodies directed against other glycolipids (11, 14, 15). No binding of antibody 101 to H2 glycolipid is detected, even with 60 pmol, suggesting that the antigens faintly detected by antibody 101 by autoradiography in glycolipids from blood group O erythrocytes (Fig. 2, lane 9) are actually H type 1 antigens and not due to cross-reaction of the antibody with the more abundant H type 2 glycolipids.

**DISCUSSION**

The two monoclonal antibodies described in this study were obtained by immunizing a mouse with the human epidermoid carcinoma cell line A431 in order to obtain antibodies to the EGF receptor. From initial screening experiments both antibodies were found to react with the cell surface of A431 cells. For these experiments the antibodies, either alone or in combination with various oligosaccharides, were incubated with cell monolayers at 4 °C for 30 min. The binding of antibodies 101 and 102 to A431 cells in the absence of oligosaccharides is shown in Fig. 4A and B. Binding of antibody 101 to A431 cells is completely inhibited by 12 mM lacto-N-fucopentaose I (Fig. 4G). Binding of antibody 101 is not inhibited by 20 mM 2'-fucosyllactose (Fig. 4C), 20 mM 3-fucosyllactose (Fig. 4E), or 12 mM lacto-N-fucopentaose II (Fig. 4F). In contrast, binding of antibody 102 is completely inhibited by 20 mM 2'-fucosyllactose (Fig. 4D). Binding of antibody 102 is not inhibited by 20 mM 3-fucosyllactose (Fig. 4F), 12 mM lacto-N-fucopentaose I (Fig. 4H), or 12 mM lacto-N-fucopentaose II (Fig. 4I).

The specificities of antibodies 101 and 102 for the human blood group H antigen were confirmed by hapten inhibition studies. The binding of antibody 101 to A431 cell membranes in solid phase radioimmunoassay is inhibited by lacto-N-fucopentaose I and not by 2'-fucosyllactose and other related oligosaccharides (Fig. 3A). In contrast, the binding of antibody 102 in the same assay is inhibited by 2'-fucosyllactose and not by lacto-N-fucopentaose I and other related oligosaccharides (Fig. 3B). Thus antibody 101 is probably directed against the human blood group H type 1 sugar sequence Fuc1-2Galβ1-3GlcNAc ... and antibody 102 is probably directed against the human blood group H type 2 sugar sequence Fuc1-2Galβ1-4GlcNAc ... (6). Monoclonal antibodies directed against the H type 2 sugar sequence have been reported previously (12, 13).

Additional evidence for the specificities of antibodies 101 and 102 were obtained from hapten inhibition studies using cultured A431 cells. For these experiments the antibodies, either alone or in combination with various oligosaccharides, were incubated with cell monolayers at 4 °C for 30 min. The binding of antibodies 101 and 102 to A431 cells in the absence of oligosaccharides is shown in Fig. 4A and B. Binding of antibody 101 to A431 cells is completely inhibited by 12 mM lacto-N-fucopentaose I (Fig. 4G). Binding of antibody 101 is not inhibited by 20 mM 2'-fucosyllactose (Fig. 4C), 20 mM 3-fucosyllactose (Fig. 4E), or 12 mM lacto-N-fucopentaose II (Fig. 4F). In contrast, binding of antibody 102 is completely inhibited by 20 mM 2'-fucosyllactose (Fig. 4D). Binding of antibody 102 is not inhibited by 20 mM 3-fucosyllactose (Fig. 4F), 12 mM lacto-N-fucopentaose I (Fig. 4H), or 12 mM lacto-N-fucopentaose II (Fig. 4I).

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That antibody 101 is directed against a carbohydrate clarifies several puzzling findings (4): antibody 101 fails to recognize the EGF receptor in cell types other than A431; the antibody gives a positive immunofluorescence reaction with some human tumor cell lines which do not have measurable EGF receptors; the number of binding sites for antibody 101 on A431 cells exceeds the number of EGF binding sites by 5-fold; and when A431 cells are incubated with EGF under conditions which cause the EGF receptor to be internalized, there is no detectably decrease in the number of binding sites for antibody 101. Taken together, these results suggested that antibody 101 recognizes a determinant that is present both on the EGF receptor and on other cell surface molecules. The
results presented here identify the other molecules as H type 1 glycolipids. This sugar sequence must be present in both the EGF receptor and in glycolipids because antibody binding to whole cells or plasma membranes is abolished by the oligosaccharide lacto-N-fucopentaose I. Furthermore, lacto-N-fucopentaose I blocks the immunoprecipitation of the EGF receptor by antibody 101. The H type 1 carbohydrate sequence is probably not present in either the EGF receptor or in glycolipids extracted from KB cells.

The present studies also clarify the antigen recognized by antibody 102. When initially tested by immunofluorescence, antibody 102 recognized a cell surface determinant present on A431 cells but absent on KB cells. However, using antibody 102 it was not possible to precipitate [35S]methionine-labeled protein. The present results explain these findings because antibody 102 recognizes glycolipids in A431 cells which contain the H type 2 sugar sequence.

The H type 1 sugar sequence present on the EGF receptor of A431 cells is not required for receptor function because it is not present on EGF receptors in other cell types. Moreover, the location of the antigen on the receptor is remote from the EGF binding site, because antibody 101 does not inhibit EGF binding nor does it mimic the effect of EGF (4).

The small amount of glycolipid antigen detected by antibody 101 compared to antibody 102 in extracts from blood group 0 erythrocytes supports the conclusion based on chemical studies that erythrocyte glycolipids contain mainly type 2 chains (16). Most blood grouping reagents used to detect the H antigen on erythrocytes are directed against the H type 2 structure (5). The H type 1 structure detected by antibody 101 is probably the human blood group Le^H antigen (17).

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