Evaluation of Chimpanzee Antiserum to Human Carcinoembryonic Antigen

Darrow E. Haagensen, Jr., Richard S. Metzgar, Wayne Sawilich, Brent Swenson, Sarah Davis, Edward Newman, Norman Zamcheck, Samuel A. Wells, Jr., and Hans J. Hansen

Department of Surgery, The Jewish Hospital of St. Louis, Washington University Medical Center [D. E. H., S. D.]; Department of Surgery, Washington University School of Medicine, St. Louis, Missouri 63110 [S. A. W.]; Department of Microbiology and Immunology, Duke University Medical Center, Durham, North Carolina 27710 [R. S. M.]; Yerkes Primate Research Center, Emory University, Atlanta, Georgia 30322 [R. S. M., B. S.]; Mallory Gastrointestinal Laboratory, Mallory Institute of Pathology, Boston City Hospital, Boston 02118 [W. S., N. Z.]; Department of Medicine, Harvard Medical School, Boston, Massachusetts 02115 [N. Z.]; and Immunomedics, Inc., Newark, New Jersey 07103 [E. N., H. J. H.]

ABSTRACT

An adult chimpanzee (Pan troglodytes) with an endogenous circulating carcinoembryonic antigen (CEA) level of 60 ng/ml was immunized s.c. with human CEA. After 1 year of immunizations, the anti-human CEA antibody titer had plateaued. This chimpanzee antiserum demonstrated high avidity specific recognition of human CEA and showed ionic strength effects for CEA recognition similar to those previously described for goat and baboon anti-CEA antisera. Radioimmunoassay of 93 human plasma samples for CEA content using chimpanzee anti-CEA versus Roche goat anti-CEA antisera gave essentially identical results (R = 0.985).

Endogenous CEA in chimpanzee blood was very poorly identified by chimpanzee anti-human CEA antisera compared to Roche goat antisera. Column chromatography of human and chimpanzee CEA in the presence of chimpanzee anti-CEA antibody showed only reactivity for the human CEA. In addition, chimpanzee antiserum had only minimal blocking effect on the binding of either goat or baboon antiserum to human CEA.

We conclude from these studies that chimpanzee anti-human CEA antiserum recognized a determinant(s) on human CEA which was different from these recognized by goat or baboon antiserum to human CEA and this determinant(s) was poorly represented on chimpanzee CEA. In contrast, the human CEA determinant(s) recognized by baboon and goat anti-CEA antisera were readily detected on chimpanzee CEA.

INTRODUCTION

CEA

CEA

One approach to developing antisera which is specific for human CEA has been immunization of nonhuman primates. Ruoslahti et al. (9) reported that CEA immunization of the Macaca irus monkey resulted in an antibody strongly reactive with the use of the low ionic strength assay of Hansen et al. (4).

Neither monkeys of the Macaca genus or the common baboon (Papio papio) have any CEA-like activity in their circulation as detected by Roche goat anti-CEA antibody (12). However, we have shown that chimpanzees (Pan troglodytes) and gorillas (Gorilla gorilla) circulate readily detectable levels (4 to 95 ng/ml) of a CEA-like substance as identified by either goat or baboon anti-CEA antisera. The chimpCEA by physical size is very similar to human CEA (12).

We report here our results on immunizing a male chimpanzee with human CEA, and characterizing the resultant antisera for reactivity with human versus chimpanzee CEA.

MATERIALS AND METHODS

Immunization Method. An adult male chimpanzee housed at Yerkes Primate Center, Atlanta, GA, was chosen for immunization with a hCEA which was purified from human colonic carcinoma metastases in liver by the procedure of Newman et al. (13). This chimpanzee at the time of initial immunization had a circulating serum level of a CEA-like substance (chimpCEA) equivalent to 60 ng/ml of hCEA (12).

For immunization, purified hCEA was prepared as an emulsion in Freund's incomplete adjuvant (Gibco, Grand Island, New York) at a concentration of 250 µg/ml with the adjuvant oil/water ratio of 3/1. Initial inoculation was 1 mg of hCEA followed by 50 µg of hCEA given at approximately 4-week intervals. The chimpanzee was bled approximately 100 ml at the time of each inoculation for evaluation of circulating serum chimpCEA level and anti-hCEA antibody titer.

Chimpanzee Anti-hCEA Antibody Titer Determination. Titration of chimpanzee antibody to hCEA in the serial immunization bleeds was performed by addition of varying dilutions of test serum bleeds to approximately 1 ng of 125I-hCEA (Roche Diagnostics, Nutley, NJ) in an assay volume of 6.5 ml of 0.01 mol/liter of ammonium acetate buffer, pH 6.75. Assay tubes were incubated overnight at room temperature (25°C). The reaction was stopped by the addition of 1 ml of zirconyl phosphate gel (Roche Diagnostics), pH 6.25, in 0.1 mol/liter ammonium acetate buffer. Background counts bound to the gel were approximately 10% of added counts. Maximal binding of 125I-hCEA was approximately 70% of added counts. This was similar to the maximal binding of Roche goat anti-hCEA to 125I-hCEA using the same assay (10). Antibody titer was calculated as the 50% point of specific counts bound and was recorded as the reciprocal of the dilution of antisera required for 50% specific binding (10).

Effect of Buffer Molarity on Antibody Binding to hCEA. The capability of chimpanzee antibody to bind 125I-hCEA was assayed in ammonium acetate buffer, pH 6.75, from 0.01 to 0.2 M. The percentage bound of 125I-hCEA for a constant amount of antibody was determined at the different buffer molarities.

CEA Assay. The CEA assay with the chimpanzee anti-hCEA antibody used Roche Diagnostics 125I-hCEA, and unlabeled hCEA standard. EDTA buffer from Roche Diagnostics was diluted 1/12 for use in the assay standard curve. An isotope dilution format of the assay was performed with 125I-hCEA, hCEA standard, and antibody added simultaneously by automatic pipetor (Pria Dilutor; Packard Instruments) to the assay tubes containing 6.5 ml of buffer. A six-point inhibition curve was generated with 1.25, 2.5, 3.75, 5.0, 7.5, and 10 ng of hCEA standard. The assay reaction was terminated after 18 h by addition of 1 ml of zirconyl phosphate gel (5). The tubes were centri-
fuged at 3000 rpm for 10 min; the supernatant was decanted and the pellets were counted.

Roche goat anti-hCEA antibody was also used to evaluate the CEA content of human and chimpanzee blood. The assay was performed in an isotope dilution format as above, except that EDTA buffer from Roche Diagnostics was diluted 1/10 for use in the standard curve buffer and donkey anti-goat vinylidene fluoride beads (Kynar, Roche Diagnostics) were added to the assay as described previously (10, 14).

Chimpanzee Serum CEA Analysis. Chimpanzee serum samples (0.5 ml each) were extracted with 1.2 mol/liter perchloric acid (PCA) by the Roche procedure. Sephadex G-50 buffer exchange columns were used to separate the chimpCEA from PCA (15). Measurement of chimpCEA content with the Roche goat anti-hCEA antibody was performed by testing 1.5-ml aliquots from the 6.5-ml PCA extract volume eluted from the buffer exchange column. Each 1.5-ml aliquot was brought up to 6.5 ml by addition of 5 ml of the Roche Diagnostics EDTA buffer diluted 1/10. This method of sample dilution resulted in a CEA assay scale of 0 to 100 ng/ml. All samples were assayed in duplicate. For the analysis of PCA extracted chimpanzee serum samples with the chimpanzee anti-hCEA antibody the entire 6.5-ml extract volume was used in the assay. This maximized assay detection of any chimpCEA activity. Blood samples analyzed for hCEA content were obtained from 93 patients with cancer, including 36 patients with colon cancer, 23 with pancreatic cancer, 17 with breast cancer, 7 with lung cancer, 3 with stomach cancer, 2 with ovarian cancer, and 1 each with testicular cancer, prostatic cancer, and brain cancer.

Human Plasma CEA Analysis. The human plasma samples were perchloric acid extracted and buffer exchanged over Sephadex G-50 columns by the Roche procedure (15). The human samples with hCEA levels below 20 ng/ml were analyzed in duplicate as the entire 6.5-ml buffer exchange volume. Samples with hCEA levels above 20 ng/ml were assayed as aliquots of the 6.5-ml extract which were brought up to volume with Roche Diagnostics EDTA buffer diluted 1/10 for assay with goat anti-hCEA antibody or diluted 1/12 for assay with chimpanzee anti-hCEA antibody.

Antibody Affinity Purification. Antibody to hCEA raised in baboon and in goat was affinity purified by passing aliquots of each of the immune sera over a Sepharose 4-B-hCEA affinity column, followed by washing the column with saline to remove unbound protein. Bound anti-hCEA antibody was eluted with 6 mol/liter guanidine-HCl, pH 7.0, then immediately buffer exchanged into saline by passage through a Sephadex G-50 buffer exchange column (16). Trace albumin and possible protease contaminants were removed from affinity purified antibody by passage over a carboxymethyl-Affi-Gel Blue column (Bio Rad, Richmond, CA). Affinity purified antibody was concentrated to approximately 1 mg/ml by ultrafiltration on a YM 30 membrane (Amicon Corp., Lexington, MA) then sterile filtered through a 0.22-

µm filter and stored at 4°C in 1 mol/liter guanidine-HCl in saline.

Biotin Labeling of Affinity Puriﬁed Antibody. Both goat and baboon antibody affinity purified anti-hCEA antibody were labeled with biotin, courtesy of Dr. Jim Whitehead, Vector Laboratory, Burlingame, CA. Immunological activity of the biotin labeled antibody was assessed by using a solid phase avidin preparation which specifically precipitated biotin labeled antibody. Ten mg of avidin (Sigma) was complexed to 100 ml of activated polyvinyl fluoride (Kynar) by the method of Newman et al. (14). The avidin-Kynar was used as a 2% suspension in 0.01 M sodium azide with 1 mg/ml albumin buffer, pH 7.0. With 500 µl of this suspension more than 100 ng of biotin labeled antibody was precipitable.

Antibody Blocking Experiments. The ability of native goat, baboon, and chimpanzee anti-hCEA antibody to block the binding of 125I-hCEA to either goat or baboon anti-hCEA antibody labeled with biotin was assessed in the following manner. The amount of each of the above antibodies required to bind 60% of 1 ng of 125I-hCEA in 6.5 ml of 0.01 M ammonium acetate buffer in a reaction time of 5 h was determined. This quantity of each of the antibodies was defined as 1 unit. Antibody blocking experiments were then conducted by first preincubating 1 ng of 125I-hCEA in 6.5 ml of 0.01 M ammonium acetate buffer with 0 to 16 units of goat, baboon, or chimpanzee antibody overnight at room temperature. This was followed by addition of 1 unit of either biotin labeled goat or baboon anti-hCEA antibody and a second incubation for 5 h. The assay was terminated by addition of 500 µl of 2% avidin-Kynar suspension to each assay tube. After a 30-min incubation the tubes were centrifuged at 3000 rpm for 10 min; the supernatant was decanted and the pellets were counted.

The percentage of inhibition of antibody binding was measured relative to the binding of 125I-hCEA by 1 unit of biotin labeled goat or baboon anti-hCEA antibody in the absence of any inhibiting antibody. This amount of binding was empirically set at 100% for determination of the degree of binding inhibition caused by the preincubation of 125I-hCEA with native chimpanzee, baboon, or goat antibody.

Column Chromatography for Sizing of Human Chimpanzee CEA in the Presence or Absence of Baboon or Chimpanzee Anti-CEA Antibody. A 2.6-x 90-cm Sephacryl S-400 column was equilibrated at 10°C with 0.9 mol/liter saline containing 0.001 mol/liter sodium azide. A 1-ml volume of chimpanzee serum, either preimmunization or after 8 months of immunization, was incubated overnight at 25°C with approximately 1 ng of 125I-hCEA, then chromatographed on the Sephacryl S-400 column. Separately, a 1-ml volume of chimpanzee serum had 7 µl of baboon anti-hCEA serum added, followed by incubation overnight at 25°C, then chromatographed as above. The serum samples were eluted from the Sephacryl S-400 column with a 90-cm gravity flow rate of approximately 40 ml/h and collected in 4.5-ml fractions. The cold chimpanzee activity in eluted fractions was determined by perchloric acid extraction of 2.5-ml aliquots from each column fraction in order to separate chimpCEA from any bound antibody and cause acid denaturation of the antibody, leaving solubilized chimpCEA after centrifugation. This method of separating CEA from antibody was initially developed for hCEA complexed to baboon anti-hCEA antibody (16). The efficiency of extraction and recovery of chimpCEA with this technique was greater than 90%. Each supernatant fraction was then buffer exchanged into 0.01 M ammonium acetate buffer, followed by determination of chimpCEA content with the Roche goat anti-hCEA antibody assay as described above. The elution of 125I-hCEA from the Sephacryl S-400 columns was determined by analyzing the number of 125I counts present in each column fraction.

RESULTS

Antibody Titer Development. The adult male chimpanzee immunized monthly with human CEA responded by the development of anti-hCEA antibody which plateaued in titer after approximately 1 year (Fig. 1). The maximal antibody titer attained in the chimpanzee was approximately 3 logs lower than that obtained in goats, and 2 logs lower than in baboons given a similar immunization regimen with the same hCEA preparation (10). During the 2-year immunization study, the chimpanzee's own level of chimpCEA-like activity in his serum showed only minimal fluctuation from the preimmunization level of 60 ng/ml (Fig. 1).

Chimpanzee Antibody Avidity. The avidity of chimpanzee anti-CEA antiserum after 1 year of immunization in comparison to goat and baboon antiserum was similar as judged by CEA inhibition curves in 0.01 M ammonium acetate buffer (Fig. 2).

Ionic Sensitivity of Antibody Binding to CEA. Comparison of chimpanzee, baboon, and goat anti-CEA antibody for binding of 125I-hCEA in the presence of increasing buffer molarity between 0.01 and 0.2 M ammonium acetate (Fig. 3) showed that, baboon, and chimpanzee antibodies to have similar degrees of inhibition in binding between 0.01 and 0.03 M buffer. However, the degree of inhibition of binding 125I-hCEA by chimpanzee antibody appeared to plateau between 0.1 and 0.2 M buffer concentration in contrast to the baboon and goat antibodies, which continued to show increasing degrees of inhibition in this buffer range.

Detection of Human CEA by Chimpanzee Anti-CEA Antibody. Ninety-three human plasma samples from patients with cancer...
Detection of Chimpanzee CEA versus hCEA by Chimpanzee Anti-hCEA Antibody. In contrast to the similar degree of detection of hCEA by goat and chimpanzee antisera, the detection of chimpanzee CEA was markedly less with chimpanzee anti-hCEA antisera compared to Roche goat antisera to hCEA (Table 1). The apparent inability of chimpanzee anti-hCEA antisera to recognize chimpanzee CEA was explored further by column chromatography. In order to demonstrate that chimpanzee anti-hCEA antibody effectively bound hCEA, we added $^{125}$I-hCEA to either the preimmune or a late immune chimpanzee serum, followed by overnight incubation at room temperature, then Sephacryl S-400 column chromatography (Fig. 5). The $^{125}$I-hCEA added to the immune chimpanzee serum eluted at a larger molecular size than the $^{125}$I-hCEA added to the preimmune serum, indicating that in the immune chimpanzee serum the $^{125}$I-hCEA had complexed to the chimpanzee anti-hCEA antibody.

The serum level of the chimpanzee's own CEA (right ordinate, O) at each bleed point was measured by RIA with Roche goat antibody used to detect the chimpCEA activity.

% of specific binding = \( \frac{\text{Counts bound - background}}{\text{Total counts added - background}} \times 100 \).

The range of hCEA levels investigated with the two reagents was from 1 to 1800 ng/ml. Also assayed with both antisera were 7 cases of hepatitis, 1 with ulcerative colitis, 1 of pneumonia, 1 of colonic polyps, and 8 cases from patients without a definite diagnosis of disease. The CEA levels on both assays for these patients also had a high degree of correlation (data not shown).

Detection of Chimpanzee CEA versus hCEA by Chimpanzee Anti-hCEA Antibody. In contrast to the similar degree of detection of hCEA by goat and chimpanzee antisera, the detection of chimpanzee CEA was markedly less with chimpanzee anti-hCEA antisera compared to Roche goat antisera to hCEA (Table 1). The apparent inability of chimpanzee anti-hCEA antisera to recognize chimpanzee CEA was explored further by column chromatography. In order to demonstrate that chimpanzee anti-hCEA antibody effectively bound hCEA, we added $^{125}$I-hCEA to either the preimmune or a late immune chimpanzee serum, followed by overnight incubation at room temperature, then Sephacryl S-400 column chromatography (Fig. 5). The $^{125}$I-hCEA added to the immune chimpanzee serum eluted at a larger molecular size than the $^{125}$I-hCEA added to the preimmune serum, indicating that in the immune chimpanzee serum the $^{125}$I-hCEA had complexed to the chimpanzee anti-hCEA antibody.

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Table 1 Comparative evaluation of chimpanzee and goat anti-CEA antibody for detection of serum levels of CEA in chimpanzees

<table>
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<th>CEA (ng/ml)</th>
<th>Chimpanzee anti-hCEA antibody</th>
<th>Goat anti-hCEA antibody</th>
<th>% detected (chimp/goat)</th>
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<td></td>
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<tr>
<td>Grip</td>
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Fig. 5. Sephacryl S-400 column chromatography elution profiles for chimpanzee serum to which was added $^{125}$I-hCEA. A, 1 ml of preimmunization chimpanzee serum had added approximately 1 ng of $^{125}$I-hCEA (125,000 cpm) followed by overnight incubation at room temperature, then application to the S-400 column along with 0.5 mg of dextran blue 2000. Each 5-ml fraction was measured for absorbance at 280 nm and for $^{125}$I-hCEA radioactivity. B, same procedure as in A, except that an immune chimpanzee serum was used.

In contrast, Sephacryl S-400 column chromatography of preimmune versus immune chimpanzee serum showed similar profiles for the chimpCEA activity in both serum samples as detected by Roche goat anti-hCEA antibody (Fig. 6, A and B). In both column profiles, there was a small amount of chimpCEA-like activity detected in the break through peak from the column; however, the main peak of chimpCEA activity was at approximately 200,000 Dalton. Thus, the chimpanzee's own CEA did not appear to be bound by the chimpanzee anti-hCEA antibody present in the immune bleed.

In order to show that chimpCEA could be complexed to antibody and this would cause it to elute in a larger size, a 1-ml aliquot of chimpanzee serum had 7 μl of baboon antisera to hCEA added, followed by overnight incubation at room temperature, then S-400 chromatography (Fig. 6C). The baboon anti-hCEA antiserum was able to complex to the chimpCEA and cause it to elute at a larger molecular size than the native chimpCEA (Fig. 6, C versus A).

Competitive Blocking Studies to Chimpanzee versus Baboon or Goat Anti-hCEA Antibody. Differences in antigenic determinant recognition on hCEA by chimpanzee versus goat or baboon anti-CEA antisera was tested by performing antigenic site(s) blocking experiments with the antisera (see "Materials and Methods"). Shown in Fig. 7 are the inhibition curves obtained when 1 unit of biotinylated goat or baboon anti-hCEA antibody was titrated against 0 to 16 units of native goat, baboon, and chimp anti-hCEA antiserum. The goat and baboon anti-hCEA antisera were much more effective in inhibiting the binding of the biotinylated antibody to $^{125}$I-hCEA than was...
the chimpanzee anti-hCEA antiserum. With 16 units of goat or baboon antiserum, the binding of 125I-hCEA had been inhibited approximately 80 to 90%. In contrast, with 16 units of chimpanzee antiserum only 55% inhibition had occurred.

Chimpanzee versus Goat Anti-hCEA Antibody Recognition of CEA Activity in Human Saliva and Bile and in Gorilla Serum. It was of interest to know if the chimpanzee antibody recognition of hCEA determinant(s) differed from Roche goat antibody with regard to the CEA-like activity found in human saliva and bile and for the CEA-like activity in gorilla serum. This was tested in RIA (see ‘Materials and Methods’) by using direct addition of the saliva or bile, and by using a PCA extract of the gorilla serum. The recognition of these CEAs was equivalent for both goat and chimpanzee antisera (Table 2).

Chimpanzee antiserum recognition of hCEA specific determinant(s) was also analyzed by competition with NCA isolated by the method of Newman et al. (13). As seen in Table 3, the chimpanzee antiserum showed minimal competition by NCA, similar to that shown by goat and baboon anti-CEA antisera.

DISCUSSION

One approach to the development of antisera specific for human CEA has been the immunization of nonhuman primates (9, 10). This approach has resulted in development of antiserum in the Macaca monkey and baboon which appears to recognize hCEA but not NCA (9, 10). In contrast, goat or rabbit antiserum raised against hCEA also shows determinant recognition for NCA (13, 17).

The baboon and Macaca monkey (both members of the family Cercopithecidae) do not have any hCEA-like activity in their blood (12). However, Engvall et al. (18) has shown the presence of an NCA-like molecule in the spleens of the Macaca monkeys. In contrast, the gorilla and the chimpanzee both have circulation blood levels of CEA-like activity which in man would be considered distinctly abnormal (average, 25 ng/ml for chimpanzee and 32 ng/ml for gorilla) (12).

We assumed that chimpanzees would probably be tolerant to this hCEA and that if a chimpanzee was immunized with human CEA he would respond to non-chimpanzee specific determinants on human CEA. Our results appear to confirm this presumption.

The immunized chimpanzee produced a comparatively low titer, high avidity antiserum to human CEA which did not cause the chimpanzee’s own circulating CEA activity to decrease (Fig. 1). Also, no clinical signs of autoimmune disease activity were noted in the chimpanzee over the 2-year immunization period. In RIA, the chimpanzee antiserum showed binding avidity for human CEA comparable to that obtained with goat or baboon antisera (Fig. 2). However, RIA recognition of chimCEA by the chimpanzee antiserum was markedly decreased compared to goat antiserum (Table 1). Column chromatographic study of the chimpanzee’s own CEA in the presence of chimpanzee antihuman CEA antiserum showed little binding by the antibody to the chimpanzee CEA (Fig. 6B). In contrast, the chimpanzee antiserum readily bound 125I-hCEA (Fig. 5B).

Competition of binding sites on human CEA by goat, baboon, and chimpanzee antisera showed the goat and baboon antisera to compete equally with one another (Fig. 7). In contrast, the chimpanzee antiserum was less effective and at an antibody concentration where the goat or baboon antiserum had blocked 90% of hCEA binding sites the chimpanzee antiserum had blocked approximately 50%.

Taken together, these data indicate that the chimpanzee has produced an antisera to human CEA which recognizes a predominantly nonchimpanzee CEA cross-reactive determinant(s). The chimpanzee antiserum is not human specific, however, because it does bind gorilla CEA (Table 2). Also, it is not cancer CEA specific because it recognizes CEA-like activity in normal human saliva and bile to the same degree as the Roche goat antiserum (Table 2). The chimpanzee antiserum does recognize a CEA “specific site” determinant since it does not show cross-reactivity with NCA (Table 3). The chimpanzee anti-hCEA antiserum also accurately reflects hCEA levels in human plasma when compared with Roche goat anti-CEA antisera (Fig. 4).

This chimpanzee antiserum to hCEA may have potential clinical relevance with regard to being a source of antibody for hCEA recognition which would have minimal differences from a human immunoglobulin. We have already shown with baboon anti-hCEA antisera that it can be given to metastatic carcinoma patients without side effects (16). However, in 9 of 14 treated patients a low level anti-baboon antibody response occurred. Presumably, development of a chimpanzee anti-hCEA antibody reagent for i.v. infusion in antibody directed imaging and/or therapy may give less likelihood of anti-antibody recognition. This hypothesis awaits testing.

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