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Differing Electrical Surface Charge and Transplantation Properties of Genetically Variant Sublines of the TA3 Murine Adenocarcinoma Tumor*

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Abstract—*Comparative measurements have been made of the transplantation and electrical surface charge properties of the near-diploid TA3-Ha ascites tumor and a new hypotetraploid ascites subline designated TA3-L. The negative surface charge density and the density of electrophoretically detectable sialic acid residues were determined to be twice as great for TA3-L as TA3-Ha cells. The two TA3 sublines were found to have identical growth properties in isogeneic mice and to exhibit progressive growth in three allogeneic strains of mice. The lethal tumor cell inoculum in allogeneic mice was lower in all cases for the TA3-L cells. From a comparison of several TA3 ascites tumor sublines, it can be concluded that their transplantability into allogeneic strains of mice is correlated with the density of negative surface charge but is independent of the degree of tumor aneuploidy.*

INTRODUCTION

THE ORIGINAL TA3 mammary adenocarcinoma tumor, which arose spontaneously as a diploid tumor in an A/HeHa mouse in 1949 [1], subsequently gave rise to two variant ascites tumor sublines with widely divergent genetic, immunological and cell surface properties: (1) the near-diploid TA3-Ha tumor (modal chromosome number = 41) produces lethal takes upon transplantation into allogeneic strains of mice and several strains of rat [2, 3], and contains at its cell surface high-molecular-weight acidic sialoglycoprotein molecules (termed epiglycanin) [4–7]; (2) the hypotetraploid TA3-St subline (modal chromosome number = 69) is specific for growth in A-strain mice [8, 9], and lacks epiglycanin at the cell surface [4, 7]. The non-specific transplantation properties of the TA3-Ha tumor have been attributed to the masking by epiglycanin of $H\text{-}2^a$ histocompatibility antigens at the cell surface [4, 7, 10]. Also associated with the presence of epiglycanin at the TA3-Ha cell surface is a high density of sialic acid residues [11, 12], receptors for *Vicia graminia* lectin [13] and a large negative electrical surface charge density relative to the TA3-St subline [9, 11].

The cytogenetic, transplantation and cell surface properties of another hypotetraploid subline of the TA3 tumor, designated TA3-L, are described for the first time in this communication. Evidence is presented for two major differences between the hypotetraploid TA3-L and TA3-St sublines: (1) the TA3-L tumor is readily transplantable into allogeneic strains of mice, and (2) TA3-L cells have a large negative surface charge and a high density of electrophoretically detectable sialic acid residues at the cell surface.

MATERIALS AND METHODS

Suppliers

Female adult (12- to 16-week-old) mice were obtained from the following sources: LAF_1, CBA

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and C57BL/6 from The Jackson Laboratories (Bar Harbor, ME); S/W mice from Simonsen Laboratories (Gilroy, CA). Medium 199 was obtained from Microbiological Associates (Bethesda, MD), ^{131}I-labeled human serum albumin from Mallinkrodt (St. Louis, MO) and *V. cholerae* neuraminidase (500 units/ml, where one unit of activity is defined as the amount of enzyme that releases 1 μg of *N*-acetylneuraminic acid from human α_1-glycoprotein in 15 min at 37°C) from Calbiochem-Behring Corporation (La Jolla, CA).

Tumor lines and transplantation procedures

Two TA3 ascites tumor sublines were propagated in isogeneic LAF_1 mice by weekly i.p. injection of 10^5 cells in a 0.1 ml volume of sterile 0.9% NaCl solution at 4°C: (1) the near-diploid TA3-Ha subline, which originated in the laboratory of Dr. T. Hauschka [1], was supplied by Dr. B. Sanford (Department of Pathology, Harvard Medical School); (2) the hypotetraploid TA3-L subline, which arose during serial transplantation of TA3-Ha tumors, was provided by Dr. G. LePage (Cancer Research Institute, University of Alberta). The etiological factor(s) responsible for the aneuploid conversion of TA3-Ha cells that occurred in LePage's laboratory is not known.

All aspects of the weekly transfer of TA3 tumors were performed under antiseptic conditions. Histological evaluations of the TA3-Ha and TA3-L ascites tumors indicated the absence of cells of non-tumor origin, e.g. host lymphocytes and macrophages. The membrane integrity of TA3 cells was assessed at the time of transfer into new hosts by their ability to exclude nigrosin dye. The superior staining characteristics of this vital dye with ascites tumor cells have been described previously [14]. Cells were examined in a hemacytometer immediately following the addition of 0.5% (w/v) nigrosin to the suspending medium. Based on an observation of the number of stained cells in a field containing 200–300 total cells, the percentage of viable cells in the transplanted inoculum was routinely >97%.

Tumor growth kinetics

Ascites tumor cell doubling times during log phase growth in LAF_1 mice were measured by a technique described previously [15]. In brief, the total number of ascites cells was determined from the product of peritoneal volume and tumor cell concentration. The peritoneal volume was determined by the isotope dilution technique using ^{131}I-labeled human serum albumin dissolved in 0.9% NaCl solution [16]. Cell concentrations were measured with an electronic counter (Coulter Electronics, Hialeah, FL). Each point of a tumor cell growth curve was determined from the average population of cells in the peritoneal cavities of 5 mice.

TD_{50} *measurements*

Transplantability of the tumor subline into isogeneic and allogeneic hosts was measured by determining the i.p. tumor cell inoculum required to produce 50% lethal takes (the TD_{50}). Tumor doses for a TD_{50} determination were prepared by serial two-fold dilutions starting from a stock cell suspension with a concentration equal to the highest dose level. Medium 199 at 4°C was used as the diluent. The highest dose level was chosen to produce 100% mortality, and a total of 6–8 graded dose levels were used for a TD_{50} determination. Each tumor dose in a 0.1 ml volume was injected i.p. into 10 recipient mice. The TD_{50} value was calculated by probit analysis from the percent mortality observed at the various dose levels over an 8-week period following tumor inoculation [17].

Karyology

Karyotyping was performed on ascites tumor cells removed from LAF_1 mice that had received an i.p. injection of 25 μg colchicine in 0.9% NaCl solution 3 hr earlier. The cells were osmotically swollen for 15 min at 37°C in 0.075 M KCl, fixed with methanol/acetic acid, stained with 2% aceto-orcein and mounted as a 'squash' preparation on microscope slides. Chromosome spreads from 50 TA3-Ha and 75 TA3-L metaphase cells were photographed at 1200 to 2000× magnification with a Zeiss phase-contrast microscope and counted.

DNA measurements

Cellular DNA content was measured by the flow microfluorometric (FMF) technique [18] using log phase ascites tumor cells fixed with 4% (w/v) formalin and stained with 0.02% (w/v) acriflavin. The total DNA content of cells in G1 phase was calculated using a secondary standard of cultured humanT-1 cells, which in G1 phase contain 14.1 ± 1.7 (S.E.) pg of DNA [19].

Microelectrophoresis

Electrophoretic mobilities of 100 individual cells per sample were measured in a Zeiss cytopherometer (Carl Zeiss Company, New York) equipped with a rectangular microelectrophoresis chamber (700 μm depth) and a $Zn/ZnSO_4$ electrode assembly [20]. Mobility measurements were made at 4.0 ± 0.1°C in a 0.14 M NaCl

solution containing 0.0067 M Sorensen's phosphate buffer (pH 7.0 ± 0.1). The low temperature of the suspending medium prevented a time-dependent decrease in mobility that was observed for dilute suspensions of both TA3-Ha and TA3-L cells during electrophoresis at 23 and 37°C [21]. The ionic strength of the electrophoresis solution was 0.15, and the associated Debye length, which is a measure of the thickness of the ionic double layer surrounding fixed charge groups at the membrane surface [22], was 0.8 nm. For each sample the cellular electrophoretic mobility was determined from a series of 100 velocity measurements on individual cells at the two stationary levels within the microelectrophoresis chamber. All measurements were made with the polarity of the applied electric field (5.5 V/cm) in alternate directions, thereby cancelling out any effect of mechanical fluid drift on the net electrophoretic velocity. Surface charge density (C/m^2) was calculated from the electrophoretic mobility ($\mu m\ sec^{-1}/V\ cm^{-1}$) using the Gouy-Chapman equation [22, 23].

Neuraminidase treatment

Prior to enzyme treatment, freshly removed ascites tumor cells were centrifugally washed once (300 ***g***, 5 min) in 15 volumes of phosphate-buffered saline. Sialic acid residues were removed by incubating the washed cells (2×10^7 cells/ml) in phosphate-buffered saline (pH 7.0) containing 100 units/ml *V. cholerae* neuraminidase for 30 min at 37°C. The cells were then washed once with phosphate-buffered saline and suspended in the electrophoresis buffer for mobility measurements. Completion of the enzyme reaction in 30 min was judged from the fact that longer incubation times did not produce a further reduction in the magnitude of the negative electrophoretic mobility. Control cell preparations were treated with neuraminidase that had been inactivated by heating at 100°C for 10 min [24]. The incubation of TA3 cells with inactive neuraminidase had no effect on the cellular electrophoretic mobility. Based on exclusion of 0.5% nigrosin dye, the enzyme-treated and control cell preparations contained >90% viable cells.

RESULTS

Cytogenetic studies

The results of cytogenetic analyses summarized in Table 1 demonstrate that the TA3-Ha and TA3-L ascites sublines have modal chromosome numbers of 41 and 77 respectively when passaged in isogeneic LAF_1 mice (an F_1 hybrid of the syngeneic A-strain mouse). All of the chromosomes were acrocentric. The modal chromosome number of 41 for TA3-Ha cells occurred with a frequency of 94%, in good agreement with the cytogenetic analysis reported by Hauschka *et al.* [3]. The TA3-L cells exhibited a much broader spread of metaphase chromosome numbers, and the mode of 77 chromosomes comprised only 20% of the total metaphase counts. The average chromosome number of TA3-L metaphase cells was 76, and 64% of the chromosome counts were in the range 70–79. Consistent with the chromosome analysis, G1 cells of the TA3-L subline were found by FMF analysis to have a 1.69 times greater content of DNA than G1 cells of the TA3-Ha subline.

Tumor transplantation studies

From the transplantation data presented in Table 1, it is evident that the TA3-Ha and TA3-L ascites tumor sublines have identical growth rates and similar TD_{50} values in isogeneic LAF_1 hosts. Both tumor lines were also transplantable into allogeneic CBA, S/W and C57BL/6 mice, with the TD_{50} values being lower in all cases for the TA3-L cells.

Electrophoretic mobilities

Based on measurements of the electrophoretic mobility, the negative surface charge density of TA3-L cells is approximately twice that of TA3-Ha cells (Table 2). If the surface charge is treated as being uniformly distributed, then the average center-to-center spacing between anionic groups is 2.5 and 1.7 nm on TA3-Ha and TA3-L cells respectively.

After removal of sialic acid residues with neuraminidase, the negative surface charge density of TA3-L cells was reduced by 49.2% while

Table 1. Cytogenetic and transplantation properties of TA3-Ha and TA3-L ascites tumors

Tumor subline	Modal chromosome number*	DNA content of G1 cells* (pg/cell)	Cell doubling time in LAF_1 mice (hr)	TD_{50} values (No. cells) LAF_1	CBA	S/W	C57BL/6
TA3-Ha	41	9.3	12	16	210	940	17,500
TA3-L	77	15.7	12	17	80	530	1,375

*Metaphase chromosome counts and the DNA content of G1 cells were measured in isogeneic female LAF_1 mice.

Table 2. Surface charge characteristics of TA3-Ha and TA3-L cells

Tumor subline	Treatment*	Electrophoretic mobility ± 1 S.D.† ($\mu m\ sec^{-1}/V\ cm^{-1}$)	Negative surface charge density ($10^{-2}\ C/m^2$)
TA3-Ha	Control	−0.499 ± 0.109	0.987
	Neuraminidase	−0.255 ± 0.068	0.504
TA3-L	Control	−1.056 ± 0.072	2.089
	Neuraminidase	−0.537 ± 0.114	1.062

*Enzyme reaction conditions are described in Materials and Methods.
†Each electrophoretic mobility is the average value and standard deviation based on 100 measurements with individual cells. Mobilities were measured at 4°C by techniques described in Materials and Methods.

that of TA3-Ha cells was lowered by 48.9% (Table 2). Again treating the surface charge as being uniformly distributed, the average center-to-center spacing between the anionic groups remaining after enzymatic removal of sialic acid residues is 3.5 and 2.4 nm on TA3-Ha and TA3-L cells respectively. From the data presented in Table 2, it can be concluded that the density of electrophoretically detectable sialic acid residues at the membrane surface of TA3-L cells is approximately twice that of TA3-Ha cells.

DISCUSSION

The existence of immunosensitive and immunoresistant sublines of the TA3 ascites carcinoma makes this system a useful model with which to study possible correlations between tumor transplantation properties and diverse cellular properties, including the degree of aneuploidy and the biochemical and antigenic characteristics of the cell surface. Comparative studies with the immunosensitive, hypotetraploid TA3-St subline and the immunoresistant, near-diploid TA3-Ha subline have demonstrated that high-molecular-weight sialoglycoprotein molecules (epiglycanin) are present in significant numbers only on the surface of the TA3-Ha cells [4, 7]. It has been proposed that epiglycanin molecules, which have a molecular weight of $\sim 5 \times 10^5$ and a rod-like conformation with a total length of ~500 nm [5], act as a surface barrier that prevents the host immune defense mechanisms from recognizing histocompatability and tumor-specific antigens at the TA3-Ha cell surface. As a consequence, TA3-Ha cells are widely transplantable into both allogeneic and xenogeneic hosts, whereas the TA3-St cells which lack epiglycanin are highly immunogenic and will produce tumors only in the syngeneic A-strain mouse.

A 22% larger negative electrophoretic mobility of TA3-Ha relative to TA3-St cells has been reported by Friberg [9], which is consistent with the greater content of sialylated macromolecules at the TA3-Ha membrane surface. The larger negative charge density of TA3-Ha cells compared to TA3-St cells has also been demonstrated from the binding of polycationic ferritin observed by transmission electron microscopy [11]. It was shown by this technique that the binding of ferritin was significantly reduced after treatment of the cells with neuraminidase, thereby indicating that a major fraction of the anionic binding sites at the surface of TA3-Ha cells are sialic acid residues. Sanford [25] originally proposed that the high density of sialic acid residues at the surface of TA3-Ha cells may lead to the masking of surface antigens, or to the electrostatic repulsion of host immune agents. This possibility seems unlikely, however, in view of serological studies which demonstrated that the expression of surface antigens on TA3-Ha cells is unaffected by the enzymatic removal of sialic acid residues [3, 26]. It currently appears more probable that the entire epiglycanin molecule, and not simply the sialic acid moieties which comprise approximately 12% of the total molecular weight [6], are reponsible for the shielding of the TA3-Ha surface antigens [4, 7, 10].

The results of our studies with a new hypotetraploid TA3 subline, TA3-L, have demonstrated that it possesses a two-fold greater negative surface charge density relative to the near-diploid TA3-Ha subline (Table 1). Approximately one-half of the difference in charge densities of the TA3-L and TA3-Ha cells is attributable to neuraminidase-susceptible sialic acid residues (Table 2). Microscopic observations have indicated that the surface area of hypotetraploid TA3-L cells is approximately four times greater than that of near-diploid TA3-Ha cells, so that the total amount of electrophoretically detectable sialic acid at the surface of the TA3-L cell is about eight times larger than the amount at the TA3-Ha cell surface. In parallel with the larger negative surface charge and sialic acid content of the TA3-

L cells, they exhibit a greater virulence than TA3-Ha cells in several allogeneic strains of mice, as indicated by the TD_{50} values presented in Table 1. In both regards, the hypotetraploid TA3-L cells are distinctly different from hypotetraploid TA3-St cells, which have a lower negative surface charge density than TA3-Ha cells and are rigorously strain-specific in their transplantation properties.

The results of several comparative studies on genetically variant TA3 ascites carcinoma sublines therefore suggest that a large negative surface charge density and content of electrophoretically detectable sialic acid residues at the membrane surface are directly correlated with a loss of transplantation specificity. The membrane content of epiglycanin found in TA3-Ha, TA3-St and several hybrid cell lines formed by fusion of TA3-Ha and embryonic fibroblast cells is consonant with our conclusions based on electrophoretic data [7]. However, these general observations apparently do not extend to the degree of malignancy expressed by non-specific TA3 sublines during growth in allogeneic hosts. As shown by Weiss and Hauschka [27], the surface charge densities of TA3-Ha cells growing in six different strains of mice were remarkably similar, despite large differences in the degree of malignancy as assessed from the host survival time following tumor inoculation.

It is also of interest to consider the observations on genetically variant TA3 tumor sublines in the context of possible relationships between tumor heteroploidy and transplantation properties. Early studies with transplanted tumors indicated that a lack of strain specificity in murine tumor lines was frequently associated with an aneuploid chromosome number [28, 29]. The TA3-St tumor provides an apparent exception to this observation insofar as it is hypotetraploid, with a modal chromosome number of 69 [9], and yet is strain-specific. Further information on the relationship between the ploidy and allotransplantability of TA3 cells has been provided by a new TA3 subline, designated TA3/MM, which was derived from TA3-St cells that had accidentally been passaged in a syngeneic A/HeHa mouse with an active pneumonia infection [30]. In contrast to TA3-St cells, the tetraploid TA3/MM cells possess epiglycanin at the membrane surface and are not strain-specific in their transplantation properties [30, 31]. The TA3/MM cells therefore resemble the hypotetraploid TA3-L cells described here in terms of their ability to grow in allogeneic hosts. Based on these comparative observations with TA3-St, TA3-MM and TA3-L cells, it would appear that the varying degree of immunoresistance exhibited by several TA3 ascites sublines during allogeneic transplantation is not directly correlated with tumor cell ploidy.

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