Correlation of the Electrophoretic Mobility and Oxygen Uptake of Ehrlich Ascites Tumor Cells

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ABSTRACT

By the use of Ehrlich ascites tumor and mouse thymic cells incubated with glucose, succinate, or 2,4-dinitrophenol, the correlation of their electrophoretic mobility and metabolic activity was studied. Ehrlich ascites tumor cells showed increased mobility associated with suppressed oxygen uptake on the addition of glucose. Neuraminidase treatment of the cells suggests that none of the removable sialic acid contributes to the observed increase in cell mobility. Furthermore, such mobility change was related to neither the high glycolytic activity of the cells nor the consequent reduction in the pH of the incubation medium. A similar increased mobility associated with suppressed oxygen uptake was observed when 0.05 mM 2,4-dinitrophenol was added to the cells. However, the addition of succinate caused decreased mobility associated with accelerated oxygen uptake. It was concluded that the suppressive change in the rate of respiration would alter the negative surface charge of Ehrlich ascites tumor cells so as to increase their mobility and, conversely, its accelerative change would cause a decrease in their mobility. On the other hand, thymic cells from normal mice did not show in the presence of glucose any changes either in their mobility or in oxygen uptake, and the changes in the rate of oxygen uptake induced by the addition of succinate or 0.05 mM 2,4-dinitrophenol did not result in any significant alterations in their mobility. Apparently, thymic cells differ from Ehrlich ascites tumor cells in biochemical characteristics as well as in cell surface properties. The mechanism of the linkage between the mobility and oxygen uptake of Ehrlich ascites tumor cells is discussed.

INTRODUCTION

It has not as yet been determined whether tumor cells differ from normal cells in the properties at their electrophoretic surface. Earlier studies with cell electrophoresis have suggested that malignant transformation is associated with an increase in negative surface charge (1). Later, such increase in cell mobility has also been reported to occur in liver cells during regeneration and postnatal growth (7) or in cultured cells with increased growth rate (19). These observations appear to suggest that the increase in negative surface charge depends upon cell growth, regardless of cell malignancy. Biochemical studies of tumor cells, on the other hand, have revealed alterations in their metabolic activity as well as in their surface properties. For example, Ehrlich ascites tumor cells have been demonstrated to exhibit a high rate of endogenous respiration, high rates of aerobic and anaerobic glycolysis, and a suppression of oxygen uptake on the addition of glucose (14-16, 24), a phenomenon known as the Crabtree effect (6). Concerning glucose metabolism, the glucose transport system at the cell surface membrane has been reported to be altered in the process of cell transformation by oncogenic viruses (11, 12). In close association with cell transformation, furthermore, changes in glycoprotein and glycolipid patterns in the surface membrane can occur (10). Thus, such biochemical alterations in the surface membrane of tumor cells would be expected to cause changes in the properties at their electrophoretic surface.

The present study deals with the relationship between the electrophoretic mobility and metabolic activity of Ehrlich ascites tumor cells in an attempt to correlate the biochemical characteristics of the cells with their electrophoretic properties. At intervals after incubation of the cells at 37°C with or without glucose, cell mobility, oxygen uptake, glucose consumption, and lactic acid production were determined. The cell mobilities were measured at 4°C throughout the present experiments. In addition, the effects of succinate (a tricarboxylic acid cycle intermediate) and DNP2 (uncoupler of oxidative phosphorylation) on the cell mobility and oxygen uptake were examined. The observations obtained with Ehrlich ascites tumor cells were also compared with those of thymic cells from normal mice.

The results reported here indicate that the mobility of Ehrlich ascites tumor cells alters in close association with the changes in the rate of oxygen uptake.

MATERIALS AND METHODS

Cells. Ehrlich ascites tumor cells were maintained by weekly i.p. inoculation of 2 x 10^6 cells into female ddN mice 6 to 7 weeks old. For experiments, the ascitic fluid was removed from the mice 5 days after the inoculation and centrifuged for 5 min at 140 x g at 4°C. The resulting cell pellet was washed 3 times by resuspension and pelleting with cold PBS. After the third washing, the cells were resuspended in cold PBS and used within 40 min after removal from the mouse. The viability of the cells was over 97%, as determined by the nigrosin exclusion test.

Thymic cells were prepared from female ddN mice 6 to 7 weeks old as follows. Thymuses from mice killed by cervical fracture were rapidly removed, placed in cold PBS, and crushed by putting them between 2 slide glasses. PBS containing both crushed thymic tissues and free thymic cells was filtered with gauze. Free thymic cells were obtained from the filtrate by centrifugation and washed 3

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times with cold PBS, as described above. The viability of the cells was over 90%.

Substrates and Metabolic Inhibitors. All substrates and inhibitors were dissolved in PBS. The final concentration of glucose was adjusted to 0.7, 5.5, or 11 mM, and that of sodium succinate was adjusted to 5, 10, or 20 mM. DNP was obtained from Tokyo Kasei Co., Tokyo, Japan, and used at a final concentration of 0.01 or 0.05 mM.

Incubation of Cells for Time Course Experiments. One ml of cold cell suspension containing $2 \times 10^4$ Ehrlich ascites tumor cells or $8 \times 10^4$ thymic cells was added to 10-ml test tubes, and another 1 ml of cold PBS containing either substrates or inhibitors or both was added to each tube. For the controls, 1 ml of PBS was added to 1 ml of cell suspension. These tubes with rubber stoppers were immersed quickly into a water bath at 37° at an angle of 45°, and the cells with air as the gas phase were incubated at this temperature with 120 cycles/min of continuous shaking. At intervals after the cells were warmed to 37°, cells were cooled immediately to 4° by placing the tubes in an ice bath.

Electrophoretic Mobility. The cells cooled to 4° at each interval after incubation at 37°, as described above, were washed once with cold PBS and resuspended in 12 ml of cold PBS. Cell mobilities were measured in PBS at 4 ± 0.2° in a microelectrophoresis apparatus (Sugiura Institute, Tokyo, Japan) of the type originally described by Bangham et al. (2). The voltage used was 5.5 V/cm. Cells were observed at a magnification of approximately 400, and the time required for moving a distance of 35 μm in both directions in the cylindrical tube was measured to 0.1 sec by a stop watch. The mean values were calculated from those obtained with 20 cells in each sample.

Determination of Glucose and Lactic Acid. The cell suspension cooled to 4° at each interval after incubation at 37°, as described above, was used for determination of both glucose consumption and lactic acid production. Glucose was determined by the method of Somogyi (22) after deproteinization (23) of the cell suspension. Lactic acid was determined with lactic acid dehydrogenase (Sigma Chemical Co., St. Louis, Mo.) (13).

Treatment with Neuraminidase. Ehrlich ascites tumor cells ($1.5 \times 10^4$) cooled to 4° at each interval after incubation at 37°, as described above, were washed once with cold PBS and then incubated in 1.5 ml of PBS at 37° for 30 min at pH 7.0 with 150 units of neuraminidase from Vibrio cholerae (Calbiochem, San Diego, Calif.) with continuous shaking. Sialic acid was determined by the method of Warren (25).

Oxygen Uptake. Oxygen uptake was measured polarographically by an oxygen consumption recorder (Yanagimoto Seisakusho Co., Kyoto, Japan) with a rotating platinum electrode, originally described by Hagihara (9). Three ml of PBS or PBS containing either substrates or inhibitors or both were put into a reaction cell. After the electrode was calibrated with PBS equilibrated with air at 37 ± 0.2°, 0.1 ml of cell suspension containing $4 \times 10^4$ Ehrlich ascites tumor cells or $6 \times 10^7$ thymic cells was added to the reaction cell, and then oxygen uptake was immediately recorded continuously.

RESULTS

Usually, the cell mobility is determined at 20–25°. At this range of temperature, cells are still metabolically active (27). As will be described below, however, no oxygen uptake occurs at 4°. When the mobility of Ehrlich ascites tumor cells was determined at this temperature at intervals after incubation at 4° or at 37° without exogenous substrates, no significant change in their mobilities at the respective temperature was observed (Table 1). This indicates that their surface charge is stable at 4 or 37° for at least 2 hr and is unaffected by changing the temperature between 4 and 37°. In the present study, therefore, the cell mobility was determined at 4° after the cells were washed with cold PBS at each interval after incubation at 37°. On the other hand, the cell mobility determined before incubation at 37° (time 0) differed in each cell preparation (see Table 1). The mean mobility of Ehrlich ascites tumor cells at time 0 was $-0.815 \mu m \cdot cm/V \cdot sec$ with a ±3% variability, based on more than 70 different experiments. As described above, however, the mobility of the cells remained reproducible at 37° for at least 2 hr. Therefore, each mobility change is shown in the following experiments by the percentage deviated from the respective mobilities at time 0.

Changes in the Electrophoretic Mobility of Ehrlich Ascites Tumor Cells Incubated with Glucose. When Ehrlich ascites tumor cells were incubated at 37° with glucose, there was a significant change in their mobility as compared to the controls (Chart 1). Incubation with 11 mM glucose produced a 9.4% increase in cell mobility at 10 min and a 15.0% increase at 20 min after incubation at 37°, as compared to that at time 0. Such increase in cell mobility appears to depend upon the glucose concentration used. No significant change in the mobility was observed when the cells were incubated at 4° with glucose.

Effects of Glucose on Sialic Acid Moieties at the Surface of Ehrlich Ascites Tumor Cells. A carboxyl group of a sialic acid at the cell surface contributes partially to the negative charge of Ehrlich ascites tumor cells (4, 18). Therefore, the amount of sialic acids at the surface of Ehrlich ascites tumor cells and their cell mobility before and after neuraminidase treatment were examined at intervals after incubation at 37° with or without 5.5 mM glucose. Regardless of the presence of glucose, as shown in Chart 2, neuraminidase treatment of the cells removed a similar amount of sialic acids resulting in a similar reduction (9 to 12%) in their mobility. The cells incubated with glucose still showed higher mobilities after neuraminidase treatment than did the enzyme-treated controls. This suggests that the increase in cell mobility on the addition of glucose is unrelated to the sialic acid which is removable by this enzyme.

Oxygen Uptake and Glycolytic Activity of Ehrlich Ascites Tumor Cells. To know whether the observed increase in mobility of Ehrlich ascites tumor cells is related to their metabolic state, the rates of oxygen uptake, glucose consumption, and lactic acid production were determined. Oxygen uptake of Ehrlich ascites tumor cells was sup-
Chart 1. Effects of glucose on the mobility of Ehrlich ascites tumor cells. Glucose or PBS (control) was added to Ehrlich ascites tumor cells at 4°, and then they were warmed quickly to 37° and incubated at this temperature with continuous shaking. In this and Charts 2, 5A, 6A, and 7A, the cell electrophoretic mobilities at each interval after incubation at 37° were measured as described in Table 1. Each mobility change is shown by the percentage deviation from the respective mobilities at time 0. Bars, S.E.

Effects of DNP on the Electrophoretic Mobility and Oxygen Uptake of Ehrlich Ascites Tumor Cells. The suppression of oxygen uptake of Ehrlich ascites tumor cells on the addition of glucose is released by DNP (14, 24). To examine in more detail the relationship between the cell mobility and oxygen uptake, Ehrlich ascites tumor cells incubated with 0.05 mM DNP in the presence or absence of pressed on the addition of glucose, depending upon its concentration (Chart 3), as originally reported by Crabtree (6). No oxygen uptake was observed when the cells were incubated at 4° with or without glucose.

The cells incubated with 0.7 mM glucose utilized the most glucose by 25 min with lactic acid production, and those incubated with 5.5 or 11 mM glucose showed continued glucose consumption and lactic acid production during the observed period (Chart 4). In these cells, however, the initial rates of glycolysis appeared similar by 10 min, at which time the cells showed increased mobilities to various extents depending upon the glucose concentration (see Chart 1). This may suggest that the initial increase in cell mobility in the presence of glucose is unrelated to the glycolytic activity of Ehrlich ascites tumor cells. Although potassium and sodium fluxes occur depending upon glycolysis, such ion fluxes do not affect the cell mobility (28).
Electrophoretic Mobility of Ehrlich Ascites Cells

The addition of both glucose and DNP, however, produced a 4.3% decrease in cell mobility at 10 min followed by an increase to the control level, in contrast to an 8.5% increase at 10 min in the presence of 5.5 mM glucose alone (Chart 5A). Such initial decrease in mobility was also observed immediately after DNP was added to the cells which were incubated previously with 5.5 mM glucose for 10 min at 37° and showing an increased mobility. Oxygen uptake of these cells was remarkably accelerated over the control.

5.5 mM glucose were examined.

On the addition of DNP to the cells, their mobility increased remarkably (Chart 5A), and oxygen uptake was suppressed 10 min after incubation, remaining at lower levels afterwards (Chart 5B) as compared to the control. DNP (0.05 mM) causes increased mobility associated with suppressed oxygen uptake. [DNP (0.01 mM) did not significantly affect either the cell mobility or oxygen uptake.]

Chart 2. Effects of neuraminidase on the mobility of glucose-stimulated Ehrlich ascites tumor cells. As described in Chart 1, Ehrlich ascites tumor cells were incubated at 37° with 5.5 mM glucose or with PBS (control). At each interval after incubation at this temperature, the cells (1.5 x 10⁶) were washed once with PBS at 4° and then treated at 37° with 150 units of neuraminidase in 1.5 ml PBS at pH 7.0 for 30 min. The cell mobilities were measured before and after neuraminidase treatment.

Chart 3. Effects of glucose on oxygen uptake of Ehrlich ascites tumor cells. Glucose or PBS (control) was added at 4° to each reaction cell containing 4 x 10⁶ Ehrlich ascites tumor cells, and oxygen uptake was recorded polarographically immediately after incubation at 37°.

Chart 4. Rates of glucose consumption and lactic acid production of Ehrlich ascites tumor cells.
Effects of Glucose, Succinate, and DNP on the Electrophoretic Mobility and Oxygen Uptake of Thymic Cells from Normal Mice. To examine the correlation of the mobility and oxygen uptake of nontumor cells, thymic cells were prepared from normal mice, since free thymic cells could be obtained with little cellular damage. Their mean mobility at time 0 was $-0.477 \text{ \( \mu \text{m} \cdot \text{cm}/\text{V} \cdot \text{sec} \)}$ with a $\pm 4.8\%$ variability.

Chart 7A shows the changes in the mobility of mouse thymic cells at intervals after incubation at 37° with 5.5 mM glucose, 10 mM succinate, and 0.05 mM DNP, respectively. Their oxygen uptake is shown in Chart 7B. On the addition of glucose, no significant changes either in the cell mobility or in oxygen uptake were observed. On the other hand, their oxygen uptake was accelerated on the addition of succinate, whereas the cell mobility did not change significantly. Similarly, DNP did not affect the cell mobility, whereas their oxygen uptake was accelerated by 10 min (release of the Crabtree effect) (Chart 5B), and their glycolysis was enhanced (Chart 5C), as compared to the cells which showed increased mobility in the presence of 5.5 mM glucose alone. The fact that Ehrlich ascites tumor cells showed either increased or decreased mobility in the process of glycolysis suggests the glycolysis independency of the changes in the mobility of the cells. Moreover, the rapid reduction in the pH of the incubation medium, which occurred depending upon lactic acid production, may be unrelated to the mobility change of the cells, since those incubated with DNP alone showed increased mobilities without changes in the pH (Chart 5D). Therefore, the initial decrease in mobility of Ehrlich ascites tumor cells incubated with both glucose and DNP may be associated with accelerated oxygen uptake.

Effects of Glucose, Succinate, and DNP on the Electrophoretic Mobility and Oxygen Uptake of Ehrlich Ascites Tumor Cells. To confirm the relationship between the decrease in cell mobility and accelerated oxygen uptake, Ehrlich ascites tumor cells incubated with 5, 10, or 20 mM succinate were examined. Depending upon its concentration, their mobility showed a 2.9 to 7.5% decrease at 10 min, remaining afterwards at lower values than the controls (Chart 6A). Such decrease in cell mobility appeared to correlate with accelerated oxygen uptake (Chart 6B). In the cells incubated with 10 mM succinate, the pH of the incubation medium increased only slightly from 7.00 at time 0 to 7.07 at 60 min.

Effects of Glucose, Succinate, and DNP on the Electrophoretic Mobility and Oxygen Uptake of Thymic Cells from Normal Mice. To examine the correlation of the mobility and oxygen uptake of nontumor cells, thymic cells were prepared from normal mice, since free thymic cells could be obtained with little cellular damage. Their mean mobility at time 0 was $-0.477 \text{ \( \mu \text{m} \cdot \text{cm}/\text{V} \cdot \text{sec} \)}$ with a $\pm 4.8\%$ variability.

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Effects of Succinate on the Electrophoretic Mobility and Oxygen Uptake of Ehrlich Ascites Tumor Cells. To confirm the relationship between the decrease in cell mobility and accelerated oxygen uptake, Ehrlich ascites tumor cells incubated with 5, 10, or 20 mM succinate were examined. Depending upon its concentration, their mobility showed a 2.9 to 7.5% decrease at 10 min, remaining afterwards at lower values than the controls (Chart 6A). Such decrease in cell mobility appeared to correlate with accelerated oxygen uptake (Chart 6B). In the cells incubated with 10 mM succinate, the pH of the incubation medium increased only slightly from 7.00 at time 0 to 7.07 at 60 min.

Effects of Glucose, Succinate, and DNP on the Electrophoretic Mobility and Oxygen Uptake of Ehrlich Ascites Tumor Cells. Either 0.05 mM DNP or 5.5 mM glucose or both were added to Ehrlich ascites tumor cells at 4°, and then they were warmed quickly to 37° and incubated at this temperature with continuous shaking. For the controls, PBS was added to the cells. A, cell mobility. B, oxygen uptake. Each reaction cell contained $4 \times 10^9$ cells, and oxygen uptake was recorded as described in Chart 3. C, rates of glucose consumption and lactic acid production. 0, changes in the pH of the incubation medium.

Chart 5. Effects of DNP on the mobility, oxygen uptake, and aerobic glycolysis of Ehrlich ascites tumor cells. Either 0.05 mM DNP or 5.5 mM glucose or both were added to Ehrlich ascites tumor cells at 4°, and then they were warmed quickly to 37° and incubated at this temperature with continuous shaking. For the controls, PBS was added to the cells. A, cell mobility. B, oxygen uptake. Each reaction cell contained $4 \times 10^9$ cells, and oxygen uptake was recorded as described in Chart 3. C, rates of glucose consumption and lactic acid production. 0, changes in the pH of the incubation medium.
and suppressed afterwards, as compared to the controls. These observations suggest that the mobility of thymic cells does not correlate with the changes in the rate of oxygen uptake.

**DISCUSSION**

Ehrlich ascites tumor cells used in the present study were prepared by washing 3 times with PBS at 4° within the first 40 min after removal from the mouse. On the basis of the following points, these washed cells appear to maintain at 37° in PBS their metabolic activity and the biophysical properties of their surface membrane: (a) the cells showed high rates of respiration and aerobic glycolysis; (b) their mobility remained reproducible for at least another 2 hr; (c) 100% of the cells showed with rapid mobility changes the ability to produce cap formation by treatment with fluorescein-conjugated concanavalin A, suggesting that their surface membrane remains biologically active in responding to concanavalin A so as to induce redistribution of its own receptors.

The present study first demonstrated electrophoretic alterations closely related to the metabolic state of Ehrlich ascites tumor cells. The surface charge of the cells remained constant as their metabolism proceeds without exogenous substrates. However, their mobility increased on the addition of glucose. It appears unlikely that such mobility change is due to the high glycolytic activity of the cells. Furthermore, the possibility that the consequent reduction in the pH of the incubation medium would induce any molecularly linked structural alterations in the cell surface so as to change the cell mobility could be excluded, since the cells incubated with 0.05 mM DNP and those with succinate showed increased and decreased mobilities, respectively, with little or no change in the pH of the incubation medium. Regardless of the substrates or inhibitors added, however, the cells with increased mobility showed suppressed oxygen uptake whereas those with decreased mobility did show accelerated oxygen uptake. Therefore, it could be concluded that the suppressive change in the rate of respiration would alter the surface charge of Ehrlich ascites tumor cells so as to increase their mobility and, conversely, its accelerative change would cause a decrease in mobility.

The mobility change observed in Ehrlich ascites tumor cells during the process of glucose metabolism appears to correspond to the biochemical phenomenon of the Crabtree effect. As described above, however, such alterations in the surface charge are related directly to the changes in the rate of respiration. Therefore, the mechanism whereby the surface charge of Ehrlich ascites tumor cells is altered may be unrelated to the mechanism biochemically proposed for the Crabtree effect (8, 14, 17, 26).

The question arises as to what mechanism is involved in the correlation of the cell mobility and oxygen uptake of Ehrlich ascites tumor cells. Two different interpretations at least can be proposed. First, any changes in cell volume would occur in close relation to the changes in the rate of respiration. Thus, the surface area and charge density could be altered. Patinkin and Doljanski (21) have reported, however, that the electrophoretic mobility of Landschütz ascites carcinoma cells and mouse leukocytes suspended in a series of solutions of differing hypotonicity remains constant in spite of increases in volume. Moreover, Nordling and Mayhew (20) have suggested that the charge density of the cell surface remains unaltered during morphological alterations in the surface area. Thus, it appears unlikely that any morphological alterations related to respiration may be responsible for the mobility changes observed in Ehrlich ascites tumor cells. Second, neuraminidase treatment of the control and glucose-stimulated Ehrlich ascites tumor cells reveals that the concentration of the removable sialic acid originally located at the electrophoretic surface of the cells is unaltered during the process of glucose metabolism (Chart 2). After neuraminidase treatment, however, the glucose-stimulated cells still showed the higher negative surface charge, as compared to the enzyme-treated control cells. Presumably, any NCB molecules other than those of the removable sialic acid may appear at the electrophoretic surface of Ehrlich ascites tumor cells in the process of glucose metabolism. Similar NCB molecules unsusceptible to neuraminidase have also been suggested to present at the electrophoretic surface of some tumor cells, such as glycogen-storing Ehrlich ascites tumor cells (3) and solid form of sarcoma 37 cells (5). The nature of the NCB molecules remains to be determined. Sialic acids unsusceptible to neuraminidase may constitute some portions of the NCB molecules (3, 5). In addition, an unidentified acid group(s) associated with a lipid system (4) and ionogenic groups susceptible to RNase (18) have been suggested to contribute to the negative surface charge of Ehrlich ascites tumor cells. Characterization of the NCB molecules is currently under investigation. Presumably, the rapid increase or decrease in mobility of Ehrlich ascites tumor cells may result from the rapid redistribution of the NCB molecules at the electrophoretic surface from the inner site to the periphery or from the periphery to the inner site of the cell membrane. Such redistribution of the NCB molecules, some of which should relate to the changes in the rate of respiration, could result from the membrane fluidity.

In contrast to Ehrlich ascites tumor cells, the changes in the rate of respiration did not alter the mobility of thymic cells, which showed a low electrophoretic mobility (−0.477), as compared to the Ehrlich ascites cells (−0.815 μm cm/V sec). In the presence of glucose, moreover, thymic cells did not show any changes either in cell mobility or in oxygen uptake. It is evident, therefore, that thymic cells differ from Ehrlich ascites tumor cells in the biochemical characteristics of glucose metabolism as well as in cell surface properties. As described above, the glucose transport system at the cell surface membrane has been suggested to be altered in the process of cell transformation by some oncogenic viruses, such as murine sarcoma virus (12) and Rous sarcoma virus (11). Such alteration has been suggested to be due to a rearrangement of membrane subunits which should relate to transformation (11). Evidence has accumulated, furthermore, that enhancement of glycolipid synthesis and changes in glycoprotein and glycolipid patterns in the surface membrane can occur in close association with cell transformation (10). It does not appear

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unreasonable, therefore, to assume that any molecularly linked structural alterations closely related to the NCB molecules described above might be induced to various extents in the cell surface membrane during the process of cell transformation.

As described above, the electrophoretic measurement at 4°C has great advantages for time sequence studies to examine the correlation of the biochemical characteristics of tumor cells and their electrophoretic mobility. Furthermore, the present observations indicate that cell electrophoresis would be an excellent tool, if combined with other biological techniques, to obtain information concerning molecularly linked structural alterations induced in the cell membrane by carcinogenic substances, such as chemical and virological agents, and to analyze the mechanism whereby the cell membrane would be altered in the process of cell transformation.

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