The demonstration of synthesis of basement membrane by parietal yolk sac epithelium (14), and the observation that this epithelial basement membrane material (EBM) is antigenically (13, 15) and chemically (11) unrelated to connective tissues, but is associated with almost all epithelia in the mouse (10), are compatible with the concept that basement membranes between epithelia and stroma are synthesized by the epithelial cells.

Most of the data on the epithelial origin of basement membranes were obtained through manipulation of a parietal yolk sac carcinoma (13-15). Since neoplastic cells are often easier to manipulate than normal ones, a study has been made of a group of murine neoplasms to determine their relationship to EBM. In the course of the study reported here, it was observed that tumors originating from epithelia which are normally associated with EBM contain EBM; moreover, 2 of these tumors synthesized EBM in tissue culture in the absence of connective tissue elements.

MATERIALS AND METHODS

Eighteen transplantable and 8 primary tumors were employed (Table 1). With the exception of the adrenal cortical carcinoma, obtained from N. El Bolkainy of this department, the teratocarcinoma, LS-402 VI A from L. C. Stevens of the Jackson Laboratory, Bar Harbor, Maine, and the reticulum cell sarcoma from M. Potter of the NIH, Bethesda, Maryland, the tumors were obtained from the Production Division of the Jackson Laboratories, Bar Harbor, Maine.

Tumor-bearing animals were killed by cervical dislocation; slabs of neoplastic tissue, 2 mm in thickness, were frozen immediately in a bath of Dry Ice and alcohol and stored at −20°C. Adjacent slabs of tissue were fixed in Bouin’s fluid and processed for routine histology.

The antibodies to epithelial basement membrane antigen (anti-EBM) that were incapable of reacting with connective tissue elements, and antibodies to collagen (anti-col) that were incapable of reacting with EBM were prepared and purified as described previously (13, 15). In addition, basement membrane antigens were extracted from the granulosa cell carcinoma (H 4929) and were used to immunize rabbits by methods described previously for the production of anti-EBM (13, 15).

For the immunohistochemical procedures the frozen tissues were cut at 6 μ, fixed in cold acetone or formalin for 10 min, and washed in 0.02 M phosphate buffered saline (PBS) at pH 7.0. They were stained by the indirect fluorescein antibody technic of Coon (3), as described previously (13, 15). The 1st serial section was stained with anti-EBM, the 2nd with anti-col, and the 3rd (control) with anti-EBM absorbed with EBM or with normal rabbit serum.

For the in vitro experiments, fragments of solid epithelial tumors were dissociated with 0.25% trypsin in Ca²⁺- and Mg²⁺-free, balanced saline solution (BSS) (9) for 1 hr with continuous gentle shaking. The resulting suspension of cells was strained through a stainless steel...
filter to remove undissociated particles, and centrifuged. The pellet was resuspended in a known volume of Ca\(^{++}\) and Mg\(^{++}\)-free BSS and the cells were counted. Appropriate dilutions were made with feeding mixture so that flat tubes and flasks received about 500,000 and 1,000,000 cells, respectively. The feeding mixture was composed of 20% fetal calf serum in Hanks's BSS to which appropriate dilutions were made with feeding mixture so that

The cultures were fed when the pH fell below 7.0 amid

1,000,000 cells, respectively. The feeding mixture was

CaD2

BW 10232

dbr B

CaD2

Primary A

Primary B

Primary C

Primary D

Primary E

Primary F

Primary G

Mammary sarcoma

Ovarian granulosa cell
tumors

H 4929

E 11731

Adrenal cortical carcinoma

E 12529

Bolkainy

Hepatoma BW 7756

Anaplastic carcinoma

15091 A

Preputial gland carcinoma

ESRI 586

Neuroblastoma C 1300

Teratocarcinoma LS 402

VI a

Melanoma H. P.

Rhabdomyosarcoma BW 10139

Reticulum cell sarcoma P 4132

Interstitial cell tumor H 10119

Tumor Strain Generation

Time (days) Presence of EBM

Mammary Carcinoma

H 2712 C3H 7 ++ +

C3HBA C3H 10 ++

BW 10232 C57BL 10 +

dbr B DBA 14 +

CaD2 DBA 7 +

Primary A C3H + + + +

Primary B C3H + + + +

Primary C A/HEJ +

Primary D CBA/J +

Primary E A/HEJ +

Primary F BALB/cJ +

Primary G A/HEJ +

Mammary sarcoma A/J —

Ovarian granulosa cell
tumors

H 4929 DBA 25-35 ++++

E 11731 A 21 +

Adrenal cortical carcinoma

E 12529 C57BL +

Bolkainy BALB/c +

Hepatoma BW 7756 C57L 21-25 +

Anaplastic carcinoma

A 10 —

15091 A

Preputial gland carcinoma

C57BL 14 +

Neuroblastoma C 1300 A 10 +

Teratocarcinoma LS 402 129 25 +

VI a

Melanoma H. P. BALB/c 14 —

Rhabdomyosarcoma BW 10139 CE 10 —

Reticulum cell sarcoma P 4132 BALB/c 10 —

Interstitial cell tumor H 10119 BALB/c 20 —

The results of the immunohistochemical survey are listed in Table 1. Tumors derived from epithelia normally associated with EBM usually contained EBM; for example, mammary carcinomas and ovarian granulosa cell tumors. Conversely, EBM was not associated with normal (10) or neoplastic liver cells, or with reticulum cell sarcoma, or rhabdomyosarcoma.

The distribution and amount of EBM varied with the individual epithelial tumors. It was most often found in delicate bands separating stroma from clumps of carcinoma cells, but occasionally it was also far removed from stroma, within masses of neoplastic cells where it surrounded alveolar aggregates or clumps of tumor cells. Thus, an organoid appearance was imparted to these tumors. On rare occasions EBM was found intimately associated with single cells or short cords of undifferentiated cells.

MAMMARY CARCINOMAS (PLATE 1)

With few exceptions, the transplanted and primary mammary carcinomas had similar histologic appearances. For the most part they were composed of lobulated masses of unoriented cells surrounded by a palisade of cells with elongated nuclei that resembled basal cells (Fig. 1). Unlike basal cell tumors, however, gland-like configurations typical of adenocarcinoma could often be seen within these masses of cells. When these tumors were stained with fluorescein-labeled antibodies to demonstrate EBM, narrow bands of specific fluorescence were observed between stromal and neoplastic elements (Fig. 4a, b, c). Not all stromal islands were outlined by EBM. Very delicate bands of EBM often surrounded the gland-like configurations in the centers of lobules.

The epithelial specificity of the anti-EBM was confirmed by the observation that the stroma was not stained by this reagent (Figs. 4, 5); anti-collagen, on the other hand, stained it brilliantly but spared the tumor cells (Figs. 4b, 5b).

Of the primary breast tumors, 1 was a sarcoma which did not contain EBM and 1 was an exceedingly anaplastic carcinoma and lacked basal cell configurations and alveolar groupings (Fig. 2). This highly malignant epithelial tumor was associated with so little EBM that it was impossible to photograph it. Another of the primary adenocarcinomas contained many glandular acini (Fig. 3); EBM separated stroma and parenchyma and outlined the glandular configurations characteristic of this pattern of neoplastic growth (Fig. 5a, b). EBM was also found surrounding small clumps of neoplastic cells that lacked acinar groupings; occasionally, single cells were invested by it. It was never seen on the luminal surfaces of acini (Fig. 5).

OVARIAN GRANULOSA CELL CARCINOMA (PLATE 2)

The granulosa cell carcinoma (H 4929) was polycystic (Fig. 6a). The larger cysts, about 1 mm in diameter, were lined by a cuboidal type of darkly stained epithelium and were separated from each other by masses of typical uniform granulosa cells which were often arranged in cords or

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sembling that of human granulosa cell tumors. The small folliculoid spaces contained eosinophilic material. The other granulosa cell tumor (E 11731) was folliculoid but lacked the larger cysts (Fig. 6b).

In the polycystic tumor, EBM was present in the walls of some of the cysts and was often interposed between stroma and neoplastic cells (Fig. 7a, b). With the exception of the parietal yolk sac carcinoma described previously, this granulosa cell carcinoma contained more EBM than any of the other neoplasms examined. The granulosa cell carcinoma (E 11731) also contained EBM which was present in small amount and was intimately associated with either single cells, or with short cords of neoplastic cells (Fig. 8a, b).

HEPATOMA BW 7756

This was a typical hepatocellular hepatoma with a cord-like arrangement of cells in which neither glandular arrangements nor bile droplets were observed (Fig. 9a). This tumor did not contain EBM (Fig. 9b). When reacted with anti-collagen, reticulin and vascular basement membranes were stained and they accentuated the organoid appearance of the tumor (Fig. 9c).

SARCOMAS (PLATE 4)

Tumors of connective tissue origin did not contain EBM (Figs. 10a, b, c, 11a, b). When they were stained with anti-collagen, fine horn-like fibrils of reticulin and a sinusoidal pattern of endothelial basement membranes were present in the reticulum cell sarcoma (Fig. 10c). The reaction of the rhabdomyosarcoma with anti-collagen was patchy (Fig. 11b). Large masses of highly malignant cells were unstained and were often surrounded by a band of densely stained elongated cells. Typically, cells were outlined by a narrow band of brilliant positive fluorescence, which appeared to coincide with the sarcolemma or basement membrane of these neoplastic muscle cells.

ADRENAL CORTICAL CARCINOMAS (PLATE 5)

EBM of the adrenal tumor (E 12529) was present in delicate lamellae in widely scattered areas of the tumor (Fig. 12a, b, c). These lamellae surrounded small clumps of tumor cells and were in turn surrounded by masses of tumor cells of similar appearance. More EBM was present in the other adrenal tumor. It outlined stromal areas and often seemed to blend with the stroma. This tumor was peculiar in that the EBM was in the form of a feltwork of fine fibrils rather than in the usual lamellar pattern (Fig. 13a, b, c).

ANAPLASTIC CARCINOMA 15091 A

This rapidly growing undifferentiated carcinoma was not associated with EBM.

TERATOCARCINOMA LS-402 VI, a

The highly malignant embryonal carcinoma cells of the teratocarcinoma were not associated with EBM. As would be expected, the small foci of parietal yolk sac carcinoma cells which these tumors contained were always embedded in EBM. Primitive neuroepithelial rosettes, glandular structures, squamous pearls, and other epithelial structures, all derived by differentiation from the embryonal carcinoma (7, 12), were also associated with EBM which morphologically resembled normal basement membranes (Fig. 14a, b, c).

IMMUNOHISTOCHEMICAL REACTIONS OF EBM OF GRANULOSA CELL TUMOR (H 4929)

Antisera obtained against the basement membrane extracts of the granulosa cell carcinoma, after suitable absorption to remove contaminating antibodies to serum proteins and stroma of the host, reacted immunohistochemically with EBM of the parietal yolk sac carcinoma. Moreover, antibody to the granulosa cell basement membrane had the identical immunohistochemical staining reactions of anti-EBM (14); it contained an antibody which reacted with basement membranes in the epithelial organs examined but which was distinct from anti-reticulin. By suitable cross absorptions, the basement membrane of the granulosa cell tumor was shown to have the same antigenic properties as EBM; antibody to granulosa basement membrane when absorbed with EBM until EBM failed to react, could no longer react with basement membranes of granulosa cells. Conversely, anti-EBM absorbed to extinction with basement membranes of the granulosa cell tumor could not react with EBM.

IN VITRO DEMONSTRATION OF BASEMENT MEMBRANE ANTIGENS

The granulosa cell carcinoma H 4929, which contained the greatest amount of EBM of any of the tumors in this study, was chosen for the initial in vitro experiments. The trypsinized cells attached readily to glass and grew as monolayers with a typical pavemented or tile-like appearance. New cells grew quickly out of small clumps of undissociated cells. These tiny clumps often contained reticulin or vascular basement membranes demonstrable with anti-collagen; however, the connective tissue elements persisted for only 1 or, rarely, 2 subcultures.

EBM was present in the cytoplasm of the pavemented epithelial cells in the explants first examined after 48 hr of culture. Intracytoplasmic EBM was distributed in a fine focal pattern reminiscent of that of the parietal yolk sac carcinoma (14), but, unlike the parietal yolk sac carcinoma, significant quantities of EBM were not secreted extracellularly. Intracellular EBM was also demonstrated in subcultures of the granulosa cell carcinoma in which no connective tissue elements could be localized with anti-collagen (Figs. 15a, b, 16a, b). After culture in vitro for 30 days, the ability to synthesize EBM was lost.

Two breast carcinomas were also grown in vitro to determine their ability to secrete EBM (Fig. 17a, b, c, d). After 1 or 2 subcultures, during which the epithelial elements outgrew the fibroblasts as described previously for the granulosa cell tumor, monolayers of tile-like cells were obtained which contained EBM in their cytoplasm. This EBM had a peculiar granular and thread-like distribution (Fig. 17c, d) that was reminiscent of the pattern of the
endoplasmic reticulum of parietal yolk sac carcinoma viewed electron microscopically (14, 15). Although the breast tumors contained less EBM in vivo than the granulosa cell tumor, they produced more EBM in vitro than granulosa cell carcinomas. Extracellular EBM was present in small amounts in the form of fine filaments. No collagen was present.

DISCUSSION

The most popular hypothesis of origin of basement membranes has been that they are formed from the ground substance of connective tissue (6). In the past few years observations have been made which are compatible with the idea that glomerular epithelium secretes at least part of the glomerular basement membrane (1, 4, 8). However, the first direct evidence that an epithelium secretes its basement membrane was obtained in a series of experiments utilizing a parietal yolk sac carcinoma (13, 15). Its cells produced large amounts of a basement membrane material in vitro in the absence of fibroblasts and other connective tissue elements. This material was localized ultrastructurally, using ferritin-labeled anti-EBM, in the endoplasmic reticulum of the epithelial cells where it was presumed to be synthesized, and in the lamina densa of 3 unrelated epithelia (13). Moreover, this antigen did not cross react with connective tissue elements and, with the use of the fluorescent antibody technic of Coon, was found adjacent to most epithelia in the mouse (10). The latter observation supported the idea that basement membranes of epithelia in general were synthesized by the adjacent epithelium.

The demonstration of synthesis of basement membrane in vitro by the cells of 2 breast carcinomas and a granulosa cell carcinoma provides a sound factual basis for this concept.

Cross absorption studies between anti-EBM and EBM of the parietal yolk sac carcinoma on the one hand and of the granulosa cell carcinoma of the ovary on the other indicate that these basement membranes have the same antigenic properties. Since the antigenic properties of renal (unpublished data), placental (13), and ovarian basement membranes are similar, it would seem reasonable to suppose that basement membranes of epithelia in general have the same antigenic composition. Whether this similarity in antigenic composition is reflected in an identical chemical composition is not known. Neither the granulosa cell nor mammary carcinomas secreted enough EBM in vitro to make chemical analyses possible. The most complete information available on the chemical composition of EBM is the analysis of Mukerjee, et al. (11) on the basement membrane secretion of parietal yolk sac carcinoma. These observations indicate that the material is a hydroxyproline-containing mucoprotein that differs markedly from reticulin and collagen in carbohydrate and amino acid content. If it is a homogeneous molecular species, then it is neither reticulin nor collagen. On the other hand, the data do not rule out the possibility that EBM is composed of 2 fractions, an antigenic hydroxyproline-containing mucoprotein fraction (EBM) synthesized by epithelium, and a tropocollagen fraction. Since the cytoplasm of parietal yolk sac cells does not stain with anti-collagen, presumably the tropocollagen would be contributed to the basement membrane by the connective tissues. Against the idea of a dual origin of basement membranes is the observation that Reichert's membrane of the placentas of rodents is synthesized between 2 layers of epithelium in the absence of any connective tissue elements (14). Furthermore, we have been unable to separate tropocollagen from EBM, irrespective of the mode of fractionation employed. Although the issue is not closed, the evidence at this time appears to favor the hypothesis that epithelial basement membranes do not contain tropocollagen.

The present study clarified the understanding of the role of basement membranes in neoplasia. This topic has been investigated ultrastructurally on carcinomas of the human cervix (2) and infiltrating carcinomas of the human breast (17). Wells and Roberts illustrated an incomplete basement membrane interposed between mammary carcinoma cells and stroma of the host (17). Similarly, Ashworth et al. (2) observed basement membranes associated with infiltrating squamous cell carcinoma of the cervix; and Frei (5) observed them in relationship to a chemically induced squamous cell tumor of mice. In interpreting these observations, Ashworth et al. and Frei have suggested that invasion occurs where the basement membrane is defective, and Ashworth et al. have gone further to suggest that the connective tissue perpetually fails in reconstruction of basement membranes. Sirtori (16) examined histochemically metastatic adenocarcinoma in a lymph node and demonstrated basement membranes around the foci of neoplastic cells. He believed that the basement membrane was produced by the interaction of an organoid, well differentiated tumor and its stroma.

Since it has been demonstrated that epithelia synthesize their basement membranes, the association of basement membranes with neoplasms would appear to be a normal function of epithelial cells that is often maintained in the neoplastic state. Accordingly, these basement membranes could in no way represent a barrier developed by the host to resist neoplastic invasion. During invasion the basement membrane must be penetrated; whether this is a purely mechanical or enzymatic process is not known.

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**Fig. 1.**—Most of the mammary carcinomas had the histologic pattern illustrated. Masses of disorganized tumor cells were surrounded by a palisade of cells reminiscent of basal cells. H and E, X 260.

**Fig. 2.**—Undifferentiated primary adenocarcinoma of the breast that contained very little epithelial basement membrane material (EBM). H and E, X 260.

**Fig. 3.**—A mammary adenocarcinoma illustrating the glandular acini and relationship of tumor cells to stroma. H and E, X 260.

**Fig. 4.**—Adjacent serial sections from a primary tumor of the breast of a BALB/c mouse. × 245. a. Incubated with anti-EBM. A lamella of EBM separates stroma (S) from the masses of neoplastic cells. A few droplets of EBM may be observed between neoplastic cells. Intracytoplasmic localization of EBM comparable to that of the parietal yolk sac carcinoma (14) has never been observed in this tumor in vivo. b. Incubated with anti-collagen. The stroma stains brilliantly; the tumor cells do not. c. The control incubated with anti-EBM absorbed with EBM to illustrate the immunologic specificity.

**Fig. 5.**—Adjacent serial sections from a primary adenocarcinoma of the breast of a CBA/J mouse. × 154. a. Incubated with anti-EBM. In addition to the lamella of EBM separating stroma (S) and neoplastic cells, glandular acini are invested by EBM which separates them from adjacent neoplastic cells. Occasionally, single cells or small groups of cells were invested by it. b. Incubated with anti-collagen. The stroma stains brilliantly; the tumor cells do not.
Fig. 6.—Typical examples of the histologic patterns of the granulosa cell tumors. H and E, X 260. a. H 4929 had gross cysts; the margin of 1 is illustrated. b. E 11731 had a microfollicular pattern and did not contain large cysts.

Fig. 7.—Adjacent sections from the transplantable granulosa cell tumor. H 4929, X 154. a. Incubated in anti-EBM. Notice the EBM in lamellar pattern in the wall of the cyst (arrow) and between the tumor cells. We have not observed EBM intracytoplasmically in this tumor. b. The control, incubated in anti-EBM absorbed with EBM to demonstrate the immunologic specificity.

Fig. 8.—Adjacent sections from the transplantable granulosa cell tumor. E 11731, X 154. a. Incubated in anti-EBM to demonstrate the distribution of EBM around the tumor cells. b. The control, incubated in anti-EBM absorbed with EBM to demonstrate the immunologic specificity.
Fig. 9.—a. A typical section of the transplantable hepatoma BW 7756. H and E, × 300. b, c. Serial sections incubated in anti-EBM and anti-collagen, respectively. The hepatoma contains no EBM but the basement membranes of sinusoids and capillaries react with anti-collagen. × 245.

Fig. 10.—a. The reticulum cell sarcoma P 4132. H and E, × 260. b, c. Serial sections incubated in anti-EBM and anti-collagen, respectively. This tumor contains no EBM but vascular basement membranes and reticulum react with anti-collagen. × 245.

Fig. 11.—a. The rhabdomyosarcoma BW 10139. H and E, × 260. b. Stained with anti-collagen. Notice the patchy nature of the reaction. × 245.
Fig. 12.—a. The adrenal tumor E 12529. H and E, × 260. 
b, c. Sections stained with anti-EBM and anti-collagen, respectively. EBM was observed rarely and invested acinar arrangements of cells. There was a well developed stromal pattern in the tumor. × 245.

Fig. 13.—a, b, c. Adjacent serial sections of the adrenal tumor (BALB/c) stained, respectively, with anti-EBM, anti-collagen, and the control with anti-EBM absorbed with EBM. EBM is found as a feltwork of fine fibrils between stroma and tumor cells. × 245.

Fig. 14.—a. Testicular teratocarcinoma of Strain 129 mice. Notice the ciliated glandular epithelium, primitive neuroepithelium, embryonal carcinoma, and mature brain tissue. H and E, × 190. b, c. Stained with anti-EBM and anti-EBM absorbed with EBM, respectively. Notice the basement membranes around the profusion of differentiated structures. × 154.
Fig. 15.—a, b. Monolayer cultures of the granulosa cell carcinoma (H 4929) stained with anti-EBM, and with anti-EBM absorbed with EBM, respectively. Notice the fine intracytoplasmic distribution of EBM; little extracellular EBM was observed in these cultures. The control (b) was negative. X 610.

Fig. 16.—a, b. Monolayer cultures of a granulosa cell carcinoma (H 4929) stained with anti-EBM, and anti-EBM absorbed with EBM, respectively. The intracytoplasmic distribution of the antigen is readily apparent in (a), whereas the control (b) contains none. X 610.

Fig. 17.—a, b. Monolayers of epithelial cells from the transplantable mammary adenocarcinoma CaD2 stained with Giemsa. X 245. c, d. Stained with anti-EBM, and anti-EBM absorbed with EBM, respectively. Note in addition to the fine focal distribution of EBM the cobweb pattern of intracytoplasmic EBM. Extracellular EBM (arrow) is also present in the form of fine threads (c). The control (d) is negative. X 385.
Basement Membranes: VI. Synthesis by Epithelial Tumors of the Mouse

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