Differential Expression of Keratins 13 and 16 in Normal Epithelium, Benign Lesions, and Ductal Carcinomas of the Human Breast

Determined by the Monoclonal Antibody Ks8.12

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ABSTRACT

Previous electrophoretic analysis has indicated that keratins 13 and 16 (K13 and K16) are not present in normal human breast epithelium, but K16 is expressed in some ductal carcinomas (Moll et al., Cell 31: 11–24, 1982). K16 may thus represent a marker for identifying a subset of ductal carcinomas and for distinguishing such tumor cells from normal cells. To explore this possibility further, we have used the monoclonal antibody Ks8.12, reportedly specific for K13 and K16 (Huszar et al., Differentiation 31: 141–153, 1986), to examine keratin expression in human breast tissues. In immunocytochemistry the antibody reacted with epithelial cells of all normal samples, hyperplasias, and fibroadenomas. The staining was moderate to strong and always heterogeneous, involving most but not all luminal cells of ducts and acini. Myoepithelial cells were never stained. Of twenty-one ductal carcinomas examined, 90% gave a very weak or no reaction. The remaining 10% of cancers exhibited moderate to strong staining in about 50% of tumor cells. Cytoskeletal polypeptides extracted from the tissues and separated by polyacrylamide gel electrophoresis were analyzed by Western blotting to identify the polypeptides recognized by Ks8.12. In samples from normal tissue and a fibroadenoma, the antibody recognized a major M, 48,000 component, a size appropriate for K16. In extracts from a hyperplasia and two of four carcinomas, the antibody detected a M, 54,000 polypeptide, as well as a M, 48,000 band, properties consistent with K13 and K16, respectively. Our results provide the first evidence indicating that K16 is present in normal as well as abnormal human breast epithelium. In addition, the data suggest that K13 may be expressed in some benign lesions and ductal carcinomas of the breast. Accordingly, Ks8.12 may prove to be useful for subclassifying ductal carcinomas and for discriminating between normal and certain benign and malignant disorders of human mammary epithelium.

INTRODUCTION

Previous electrophoretic studies have identified eight keratins in the ducts of the normal human mammary gland (1). Three of these, keratins 5, 7, and 8, belong to the family of basic keratins, while five keratins, 14, 15, 17, 18, and 19, are members of the family of acidic keratins (1). Ductal carcinomas of the breast were divisible into two groups on the basis of their keratin expression (1, 2). The type I ductal carcinomas had keratins 7, 8, 18, and 19, while the type II carcinomas contained keratins 6, 7, 8, 11, 14, 16, 17, 18, and 19 (1). Thus, all of the carcinomas studied had lost expression of keratins 5 and 15, the type I carcinomas were additionally missing keratins 14 and 17, and the type II carcinomas had gained expression of keratins 6, 11, and 16.

The differential expression of keratins between normal tissues and their tumors has been found in several epithelia (1–6). Such differences represent potential markers for distinguishing between normal and tumor cells if appropriate antikeratin antibodies were available. While several antikeratin antibodies have been derived that can subdivide breast ductal carcinomas according to cell type composition, i.e., the percentage of epithelial and myoepithelial cells (7–14), none can discriminate between normal and tumor cells. The electrophoretic results with breast tissue (1) suggest that K16 might represent a marker capable not only of identifying a subset of ductal carcinomas but also of distinguishing such tumor cells from normal cells.

Recently, a MAb designated Ks8.12 was developed and reported to be specific for keratins 13 and 16 (15–17). K13 has been found only in noncornified squamous epithelia and has not been detected in normal or abnormal mammary epithelium of humans (1, 16). Accordingly, this antibody should be specific in the breast for K16, which is an acidic M, 48,000 protein (1). The availability of Ks8.12 affords the opportunity for a more detailed study of K16.

In the present investigation, we have used Ks8.12 in immunocytochemical and immunoblot procedures to examine keratin expression in epithelial cells of normal human breast and of benign and malignant disorders of the gland. The purpose was to compare the reactions of normal and abnormal mammary tissues with the antibody and to confirm the identity of the reactive component, if any, as K16. Unexpectedly, in immunocytochemistry the antibody recognized a large subpopulation of luminal cells in all normal and hyperplastic tissue and in benign tumors of the mammary gland. In contrast, only some cells in a small minority of infiltrating ductal carcinomas were reactive with the antibody. Western blot analysis revealed that Ks8.12 recognized a M, 48,000 polypeptide, a size appropriate for K16, in cytoskeletal extracts from all breast tissues examined and a M, 54,000 polypeptide, a size compatible with K13, in extracts isolated from a hyperplasia and two of four ductal carcinomas of the gland.

MATERIALS AND METHODS

Breast Tissues. Human breast tissues were obtained from surgical specimens at the Beth Israel Hospital in Boston, MA, and were processed as described previously (18). The specimens for this study included 8 samples of "normal" human mammary tissue taken from reduction mammoplasties, 5 fibroadenomas, 7 hyperplasias, and 21 infiltrating "not otherwise specified" ductal carcinomas.

Cell Culture. The human epidermoid carcinoma cell line A-431 was grown in a medium consisting of 47.5% Dulbecco's modified Eagle's medium and 47.5% Ham's F12 medium supplemented with 5% fetal bovine serum (Gibco, Inc., Grand Island, NY).

Antibodies. The mouse monoclonal antikeratin antibody Ks8.12 was prepared against bovine muzzle prekeratin and was purchased from ICN Immunobiologicals (Lisle, IL). Its derivation and characterization have been published (16). The antibody was supplied in ascites fluid, and a 1:20 working dilution was used in the present study. A sheep anti-mouse immunoglobulin antiserum conjugated with horseradish peroxidase was used as the secondary antibody.

Received 4/5/88; revised 7/6/88; accepted 7/14/88.

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1 Supported by NIH Grant CA 32937.

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3 The abbreviations used are: K16, keratin 16 (K13 defined similarly); MAb, monoclonal antibody; PAGE, polyacrylamide gel electrophoresis.

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Cancer Research 48: 5831-5836, October 15, 1988
Peroxidase (Cooper Biomedical, Inc., Malvern, PA) was used as the secondary reagent at a 1:400 dilution. The monoclonal antikeratin antibodies AE2 and AE3 have been extensively characterized (5, 19) and are used as negative and positive controls, respectively. AE2 is specific for the high-molecular-weight keratins (M, 66-67,000 and M, 56,000) found in epidermis, while AE3 recognizes an epitope present on all basic (type II) keratins (5, 19). These antibodies were generously provided by Dr. T-T. Sun. In this study AE2 was obtained in supernatants of hybridoma cultures and was undiluted, while AE3 was supplied in ascites fluid and used at a 1:50 dilution.

Indirect Immunocytochemistry. Tissue specimens were fixed in absolute ethanol, embedded in paraffin, and sectioned at a thickness of 4 to 6 μm according to the method described in Ref. 20. After deparaffinization and a brief pretreatment with Pronase (Calbiochem, La Jolla, CA) as reported in detail elsewhere (18), the sections were stained by indirect immunoperoxidase using diaminobenzidine (Sigma Chemical Co., St. Louis, MO) as the substrate for color development. Some tissue samples were also stained without the Pronase pretreatment. These sections always contained a greater number of negative cells than did sections of the same tissue treated with the enzyme (data not shown).

Finally, the sections were lightly counterstained with hematoxylin. Two pieces from separate parts of the tissue were processed and examined from each specimen. Sections sequential to those used for immunoperoxidase staining were stained with hematoxylin and eosin to confirm the histology.

Extraction of Tissues and Cultured Cells. Cytoskeletal fractions enriched in intermediate filaments were extracted from tissues and the A-431 cell culture line by the method of Franke et al. (21) with modifications described previously (22). Samples of tissues were first delipidized by treatment with ethyl acetate/acetone.

Gel Electrophoresis and Immunoblotting Analysis. Pellets of cytokeratin extracts were prepared for one-dimensional PAGE by solubilizing at 55 mg/ml (wet weight) for A-431 cells and at 200 mg/ml, 250 mg/ml, or 400 mg/ml (wet weight) for tissues as described in Ref. 22. Electrophoresis was performed according to the method of Laemmli (23) with modifications published elsewhere (22), except that minigels (7.5 cm x 10 cm; Bio-Rad, Richmond, CA) were used.

Polypeptides isolated from a hyperplasia showed that the antibody reacted with major M, 48,000 and a faint M, 45,000 and 43,000 bands that were recognized by AE2 and AE3. Proteins bands were located by India ink staining (26) of the blot after the immunoperoxidase reaction had been photographed.

RESULTS

Reactions of Ks8.12 in Immunocytochemistry. Table 1 summarizes the types and numbers of samples of human breast tissues that were examined and the staining patterns produced by Ks8.12. AE2, used as a negative control, did not react with any breast tissue samples (data not shown), consistent with its reported specificity for the high-molecular-weight keratins of epidermis (19).

Normal Epithelium. In all normal human breast tissue examined, the MAb Ks8.12 stained luminal cells exclusively. The staining pattern was heterogeneous with positive and negative cells occurring adjacent to one another (Fig. 1). There were also areas where all luminal cells were reactive adjacent to regions of completely negative cells. In each sample tested, approximately 40 to 60% of the luminal cells of both ducts and acini were positive, with the intensity of staining ranging from moderate to heavy. Myoepithelial cells were always unstained. In benign and malignant tumors, the same pattern of staining was found in ducts and acini of normal appearing areas.

Hyperplasias and Fibroadenomas. The reaction of Ks8.12 with hyperplastic tissue and fibroadenomas was also confined to luminal epithelial cells (Figs. 2 and 3). As in normal samples, the staining in most of these specimens was very heterogeneous, with approximately 40 to 60% of the cells exhibiting a moderate to heavy reaction. Two of the fibroadenomas, however, had staining in about 80 to 95% of the luminal cells.

Infiltrating Ductal Carcinomas. Of the carcinomas examined, 90% gave a very weak or no reaction. An example of an unreactive specimen, which represented 71% of the total examined, is shown in Fig. 4a. An example of a tumor with very weak reactivity, which included 19% of the total samples, is presented in Fig. 4b. Only 10% of the cancer specimens had a strong reaction, involving mainly the infiltrating component wherein approximately 40 to 60% of the tumor cells stained moderately to heavy (Fig. 4c). Some cells of the intraductal component were also stained by the antibody.

Western Blot Analysis of Cytoskeletal Extracts. To determine what component(s) in the various breast tissues was reactive with Ks8.12, Western blotting was performed using the antibody to stain proteins in cytoskeletal extracts isolated from the different breast specimens. Polypeptides in cytoskeletal fractions were separated by PAGE, electroblotted onto nitrocellulose, and stained by indirect immunoperoxidase. No reactions were obtained in any sample with the MAb AE2. The results with Ks8.12 are summarized in Table 2. The reactions of the breast samples were compared to that of a cytoskeletal fraction from A-431 cells (Fig. 5, Lane 1), which have been shown to contain keratin 13 (M, 54,000) as a major component (1, 16) and keratin 16 (M, 48,000) as a minor component (1). In one-dimensional immunoblotting, Ks8.12 detected a major M, 54,000 band and a faint M, 48,000 band. On two-dimensional blots Ks8.12 also recognized two polypeptides with molecular weights 54,000 and 48,000, both with an approximate isoelectric point of 5.1, features compatible with those of K13 and K16 (1, 16), respectively (Fig. 6).

Normal Tissue. A cytoskeletal extract prepared from normal human breast tissue contained a major M, 48,000 band and minor M, 45,000 and 43,000 bands that were recognized by Ks8.12 (Fig. 5, Lane 2).

Hyperplasias and Fibroadenomas. Analysis of cytoskeletal polypeptides isolated from a hyperplasia showed that the antibody reacted with major M, 54,000 and 48,000 bands (Fig. 5, Lane 3). A preparation from a fibroadenoma had major M, 50,000 and 48,000 bands recognized by Ks8.12 (Fig. 5, Lane 4).

Infiltrating Ductal Carcinomas. Cytoskeletal polypeptides extracted from four different infiltrating ductal carcinomas were also analyzed. These samples were chosen on the basis of the tumor’s reactivity with Ks8.12 in immunocytochemistry. M, 50,000 and 48,000 polypeptides were the major reactive components (Fig. 5, Lane 5) in a preparation from ductal carcinoma 1, which contained <0.1% tumor cells poorly stained with the MAb in immunocytochemistry. Tumor Sample 2, which had only a small minority (1%) of weakly positive tumor cells by immunocytochemistry, had major M, 54,000 and 48,000 bands recognized by Ks8.12 (Fig. 5, Lane 6). A prominent M, 54,000 band was detected by the MAb (Fig. 5, Lane 7) in tumor Sample 3, which contained by immunocytochemistry approximately 5 to 10% reactive tumor cells as well as reactive normal structures. The MAb detected bands with molecular weights of 50,000, 48,000, and 43,000 (Fig. 5, Lane 8) in a...
KERATINS 13 AND 16 IN HUMAN BREAST EPITHELIUM

Table 1 Summary of immunocytochemical reactions of human breast epithelial cells with the monoclonal antibody Ks8.12

<table>
<thead>
<tr>
<th>Tissue type</th>
<th>Positive samples/total samples</th>
<th>Reaction*</th>
<th>Staining pattern</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal Ducts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal cells</td>
<td>8/8</td>
<td>3+</td>
<td>Heterogeneous staining both within and between structures</td>
</tr>
<tr>
<td>Myoepithelium</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Alveoli</td>
<td></td>
<td>3+</td>
<td></td>
</tr>
<tr>
<td>Luminal cells</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Myoepithelium</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Hyperplasias</td>
<td>7/7</td>
<td>3+</td>
<td>Reaction same as normal</td>
</tr>
<tr>
<td>Luminal cells</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Myoepithelium</td>
<td></td>
<td>3-4+</td>
<td>Reaction same as or stronger than normal</td>
</tr>
<tr>
<td>Fibroadenomas</td>
<td>5/5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Luminal cells</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Myoepithelium</td>
<td></td>
<td>3-4+</td>
<td></td>
</tr>
<tr>
<td>Infiltrating ductal carcinomas</td>
<td>6/21</td>
<td>1+</td>
<td>Weak reaction</td>
</tr>
<tr>
<td></td>
<td>4/21</td>
<td>3+</td>
<td>Heterogeneous reaction</td>
</tr>
<tr>
<td></td>
<td>2/21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* 0, no reaction; 1+, <10% of cells stained; 2+, 10 to 40% of cells stained; 3+, 41 to 60% of cells stained; 4+, 61 to 95% of cells stained.

Fig. 1. Normal epithelium in breast tissue from a reduction mammoplasty stained by indirect immunoperoxidase with Ks8.12 and counterstained with hematoxylin. A normal duct (a) and several acini and a small duct (b) show a heterogeneous reaction. Open arrowheads point to the nuclei of unstained myoepithelial cells. Dark arrowheads point to examples of unstained luminal cells. Bar, 50 μm.

Fig. 2. Hyperplastic tissue stained by indirect immunoperoxidase with Ks8.12 and lightly counterstained with hematoxylin. In this example, almost all luminal cells are stained. The myoepithelium is unreactive. Bar, 50 μm.

DISCUSSION

Previous electrophoretic studies have revealed that K13 is expressed in normal epithelium of the anal canal, exocervix, tongue, epiglottis, esophagus, trachea, axilla, apocrine gland, bladder, and in cloacogenic carcinomas and cultured A-431 cells (1). K16 has been found in normal epithelium of foot sole, anal canal, hair follicles, exocervix, tongue, epiglottis, esophagus, and in squamous cell carcinomas of the skin, tongue, epiglottis, esophagus, and the rectal-anal region, as well as in adamantinomas and cultured A-431 cells (1). The same study also indicated that K13 is absent in the breast and K16 is present in only a subset of breast ductal carcinomas. Huszar et al. (16) tested the MAb Ks8.12 in Western blotting against all of the known human keratins and found that it recognized only Mf, 54,000 and 48,000 polypeptides which were identified as K13 and K16, respectively.

Contrary to expectations based on Moll's electrophoretic studies, our data with Ks8.12 provide evidence for the presence of K16 in normal and abnormal human breast epithelium. In addition, K13 may be expressed in some hyperplasias and ductal cytoskeletal fraction prepared from carcinoma 4, which by immunocytochemistry contained 41 to 60% reactive tumor cells along with reactive normal structures.
Table 2  Summary of immunoblot reactions of the monoclonal antikeratin antibody Ks8.12

<table>
<thead>
<tr>
<th>Cytoskeletal source</th>
<th>No. of samples</th>
<th>% of epithelial cells positive in immunocytochemistry</th>
<th>M, of reactive polypeptides</th>
</tr>
</thead>
<tbody>
<tr>
<td>A-431 cells</td>
<td>1</td>
<td>ND&lt;sup&gt;5&lt;/sup&gt;</td>
<td>54,000</td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
<td>41-60&lt;sup&gt;4&lt;/sup&gt;</td>
<td>48,000</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>1</td>
<td>41-60&lt;sup&gt;4&lt;/sup&gt;</td>
<td>48,000</td>
</tr>
<tr>
<td>Fibroadenoma</td>
<td>1</td>
<td>61-95&lt;sup&gt;4&lt;/sup&gt;</td>
<td>48,000</td>
</tr>
<tr>
<td>Ductal carcinoma 1</td>
<td>1</td>
<td>&lt;0.1&lt;sup&gt;4&lt;/sup&gt;</td>
<td>50,000</td>
</tr>
<tr>
<td>Ductal carcinoma 2</td>
<td>1</td>
<td>1&lt;sup&gt;5,10&lt;/sup&gt;</td>
<td>54,000</td>
</tr>
<tr>
<td>Ductal carcinoma 3</td>
<td>1</td>
<td>5-10&lt;sup&gt;4&lt;/sup&gt;</td>
<td>48,000</td>
</tr>
<tr>
<td>Ductal carcinoma 4</td>
<td>1</td>
<td>41-60&lt;sup&gt;4&lt;/sup&gt;</td>
<td>48,000</td>
</tr>
</tbody>
</table>

<sup>4</sup> Polypeptides in cytoskeletal fractions were separated by one-dimensional PAGE, electroblotted onto nitrocellulose, and stained by indirect immunoperoxidase with the Ks8.12.
<sup>5</sup> ND, not done.
<sup>6</sup> Percentage of luminal epithelial cells stained by Ks8.12 in immunocytochemistry (see Figs. 2 to 4; Table 1).
<sup>7</sup> Percentage of carcinoma cells stained by Ks8.12 in immunocytochemistry (see Fig. 5 and Table 1).

Fig. 3. Breast fibroadenoma stained by indirect immunoperoxidase with Ks8.12 and counterstained with hematoxylin. Open arrowheads point to the nuclei of unstained myoepithelial cells. Dark arrowheads point to examples of unstained luminal cells. Bar, 50 μm.

Fig. 4. Examples of infiltrating ductal carcinomas displaying a negative reaction (a), weak positive reaction (b), and a moderate-to-strong reaction (c) in indirect immunoperoxidase staining with Ks8.12. In a, no cells are reactive with the antibody. The open arrowhead points to an example of a nucleus which is lightly counterstained with hematoxylin. In b, the dark arrowhead points to an example of a lightly stained tumor cell, while the open arrowhead points to an unstained tumor cell. In c, open arrowheads point to the nuclei of unstained tumor cells, the dark arrowhead to a lightly stained tumor cell, and the dark arrow to a more heavily stained tumor cell. Bar, 50 μm.

Fig. 5. Immunoblot comparison of the keratins recognized by Ks8.12 in A-431 cells and tissue samples of human breast. Cytoskeletal polypeptides extracted from A-431 cells (Lane 1), normal tissue (Lane 2), a hyperplasia (Lane 3), a fibroadenoma (Lane 4), and four different ductal carcinomas [Lane 5, No. 1; Lane 6, No. 2; Lane 7, No. 3; Lane 8, No. 4 (see Table 2)], were separated by one-dimensional sodium dodecyl sulfate-PAGE, transferred electrophoretically onto nitrocellulose, and stained by indirect immunoperoxidase. Molecular weight standards are indicated (M, x 10<sup>3</sup>). a, immunoblot reaction (see Table 2 for summary); b, India ink staining of the same blot to visualize total proteins present.

carcinomas. A M, 48,000 polypeptide, consistent with K16 (1, 16), was found in all breast samples, whether normal or pathological, analyzed by immunoblotting. A M, 54,000 polypeptide, a size appropriate for K13 (1, 16), was detected in a hyperplasia and in two of the four ductal carcinomas examined, but was not found in normal tissue. It is possible that the M, 50,000 band found as the largest component in the fibroadenoma and in two of the cancers may be a degradation product.
of the M, 54,000 molecule, even though the latter polypeptide was not detected in these samples. The various other bands seen in the normal and abnormal samples probably also represent proteolytic derivatives of either the M, 54,000 or 48,000 polypeptides. The lack of K13 in the sample of normal breast was consistent with the recent report by van Muijen et al. (27), which showed that two MAbs monospecific for K13 failed to react with normal ductal epithelium of the breast in immunocytochemistry. Breast carcinomas were not included in the latter study (27), but neither Moll et al. (1) nor Huszar and coworkers (16) detected K13 in the breast carcinomas they examined.

The pattern of immunocytochemical staining with Ks8.12 in the cancers appeared unrelated to the immunoblot results in our study. That is, the tumors which had the M, 54,000 cytoskeletal polypeptide contained 1 to 10% cells positive in immunocytochemistry, whereas the carcinomas lacking this component had in one case <0.1% reactive cells and in the other case 50 to 60% reactive cells. The biological significance of the difference in keratin expression between tumors that have a subset of cells reactive in immunocytochemistry with Ks8.12 and those that do not is unknown. We are currently conducting a study to determine if the reaction of a tumor with Ks8.12 has any relationship to its clinical behavior or to a particular pathological feature relevant to prognosis.

Although the majority of cancer cells were unreactive with the Ks8.12 MAb as were all myoepithelial cells in normal epithelium and benign disorders, we do not interpret this similarity to imply that the myoepithelial cell is the cell of origin for such tumors. Previous studies using several markers for myoepithelial cells, including three different antikeratin MAbs, have indicated that myoepithelial cells are not found in the majority of ductal carcinomas and represent a subpopulation in others (e.g., 10–13). Only about 5% of ductal carcinomas appear composed almost entirely of cells which have retained the phenotype of myoepithelium (10–13). In fact, a MAb that recognizes keratin 14 (K14) in a complex with keratin 5 (K5) and preferentially detects myoepithelial cells has recently been shown to facilitate discrimination between benign and malignant human breast lesions (28).

The biological implications of the reactive and unreactive cells in normal and tumor tissue are also unknown. Several situations are possible. For example, expression of a keratin, presumably K16, reactive with Ks8.12 may be related to the state of differentiation among normal luminal cells. A more differentiated cell may have K16 either present or absent, while its less differentiated counterpart would have the opposite. Alternatively, the difference in keratin expression may be due to a difference in the stage of the cell cycle among cells. Additional samples of normal breast tissue must be analyzed to confirm whether K13 is always lacking in normal epithelium. Our data show that Ks8.12 cannot be considered a specific probe for noncornified stratified squamous cell differentiation and carcinogenesis as suggested by Huszar et al. (16). The mammary gland is classified as a simple epithelium histologically, although it has a surprisingly complex pattern of keratin expression. To date, keratins 5 and 14 have been detected in myoepithelial cells (10, 11, 13, 14, 28) while keratins 7, 8, 15, 18, 19, and now 16 have been found in luminal cells of the normal human breast (7, 8, 12, 13, 18, this report).

In summary, regardless of the molecular explanations underlying our immunological results, Ks8.12 holds promise in defining a subset of ductal carcinomas and perhaps in distinguishing between normal and benign cells and the majority of breast cancer cells. Moreover, our studies with the MAb imply that K16 is present in normal as well as abnormal breast epithelium. In contrast, K13 appears to be absent in the normal gland but may be expressed in some benign and malignant disorders. Antibodies that are monospecific for K13, such as those recently described by van Muijen et al. (27), should provide valuable tools for further exploration of this possibility.

ACKNOWLEDGMENTS

We are grateful to Dr. Tung-Tien Sun for his contribution of the AE2 and AE3 antibodies and to Leon Hall III for excellent technical assistance.

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