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*Original Articles*

# Myofibroblasts and Myoepithelial Cells in Human Breast Carcinoma

## An Ultrastructural Study

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**Summary.** Ultrastructural studies of 11 human breast carcinomata revealed that most stromal cells could be arranged in a cell spectrum from fibroblasts, with abundant rough endoplasmic reticulum, to myofibroblasts. In 4 out of 11 cases, myoepithelial cells were observed in the parenchyma at the periphery of some carcinomatous duct-like structures or carcinoma cell nests. The distinction between myofibroblasts and myoepithelial cells was usually easy from their respective locations. Their ultrastructural features were summarized as follows. Myofibroblasts: (1) abundance of rough ER and other cytoplasmic organelles; (2) bundles of microfilaments, 50–70 Å in diameter and associated dense bodies. Myoepithelial cells: (1) bundles of microfilaments 50–70 Å in diameter and associated dense bodies (a common feature); (2) dense bundles of tonofilaments, 80–100 Å in diameter; (3) typical desmosomes which connected them with adjacent myoepithelial or carcinoma cells. Myofibroblasts were occasionally located closely contiguous with carcinoma cells, giving an appearance resembling myoepithelial cells. Even in these instances a distinction between myofibroblasts and myoepithelial cells was possible, since myoepithelial cells had dense bundles of tonofilaments and typical desmosomes, which were not observed in myofibroblasts. No cell types intermediate between myofibroblasts and myoepithelial cells were detected. We could not decide whether myoepithelial cells were neoplastic or not despite the facts that they showed obscured polarity and had partially or completely lost their basal lamina. We conclude that fibroblasts, myofibroblasts and probably some, if not all, smooth muscle cells belong to the same cell system. Myofibroblasts in our material are derived from fibroblasts, while myoepithelial cells are epithelial in origin.

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## Introduction

In a previous report the authors described the occurrence of myofibroblasts in the stroma of human breast carcinoma (1979) but we did not describe fully the relationship between myofibroblasts and fibroblasts. Myoepithelial cells, which also containing bundles of microfilaments and dense bodies, have been observed in the mammary duct system and its carcinomas and we have considered the question of whether or not myofibroblasts can be transformed into myoepithelial cells, or vice versa, in human breast carcinoma. The present paper deals with the ultrastructural details of myofibroblasts and myoepithelial cells, the relationship of myofibroblasts to fibroblasts and smooth muscle cells, and the possibility of transformation between myoepithelial cells and myofibroblasts.

## Materials and Methods

Specimens of tumor tissue were obtained from surgical material from one intraductal papillomatosis, one intraductal carcinoma, and 10 invasive ductal carcinomas. For normal controls, specimens were obtained from glandular tissue adjacent to a lipoma in one case and to fibroadenomata in 3 cases.

These specimens were immediately fixed in 5% glutaraldehyde-4% paraformaldehyde in 0.08 M Na cacodylate buffer, pH 7.0–7.4. After postfixation in 1% osmium tetroxide for 2 h at 4° C, the specimens were dehydrated in graded ethanols and embedded in Epon. In some cases the specimens were divided into two groups. One group was processed as described above, and the other group was stained en bloc after postfixation with 1 or 2% aqueous uranyl acetate for 45 min. Thick sections of 1 μm were stained with toluidine blue for light microscopy to select proper areas for electron microscopy. Thin sections of 600–900 Å were cut with glass or diamond knives on a Porter-II ultramicrotome, stained with uranyl acetate and lead citrate, and examined with a JEOL 100B electron microscope accelated at 80 or 100 KV.

## Results

### *Myofibroblasts*

In all cases of breast carcinoma, most stromal cells of spindle shape were observed to have well-developed rough endoplasmic reticulum and Golgi-apparatus. They also had many free ribosomes and vesicles, some of which were coated. The cisternae of rough endoplasmic reticulum were sometimes dilated and filled with material of moderate electron density. In addition, a few narrow bundles of microfilaments, 50–70 Å in diameter, were usually contained in these cells, running mainly beneath the cell membrane and longitudinally along the cell axis. Dense bodies were distributed along each bundle. The amount of microfilaments varied from one stromal cell to another. When they contained few definite bundles of microfilaments, the cells exhibited the typical structures of activated fibroblasts; whereas cells equipped with a considerable number

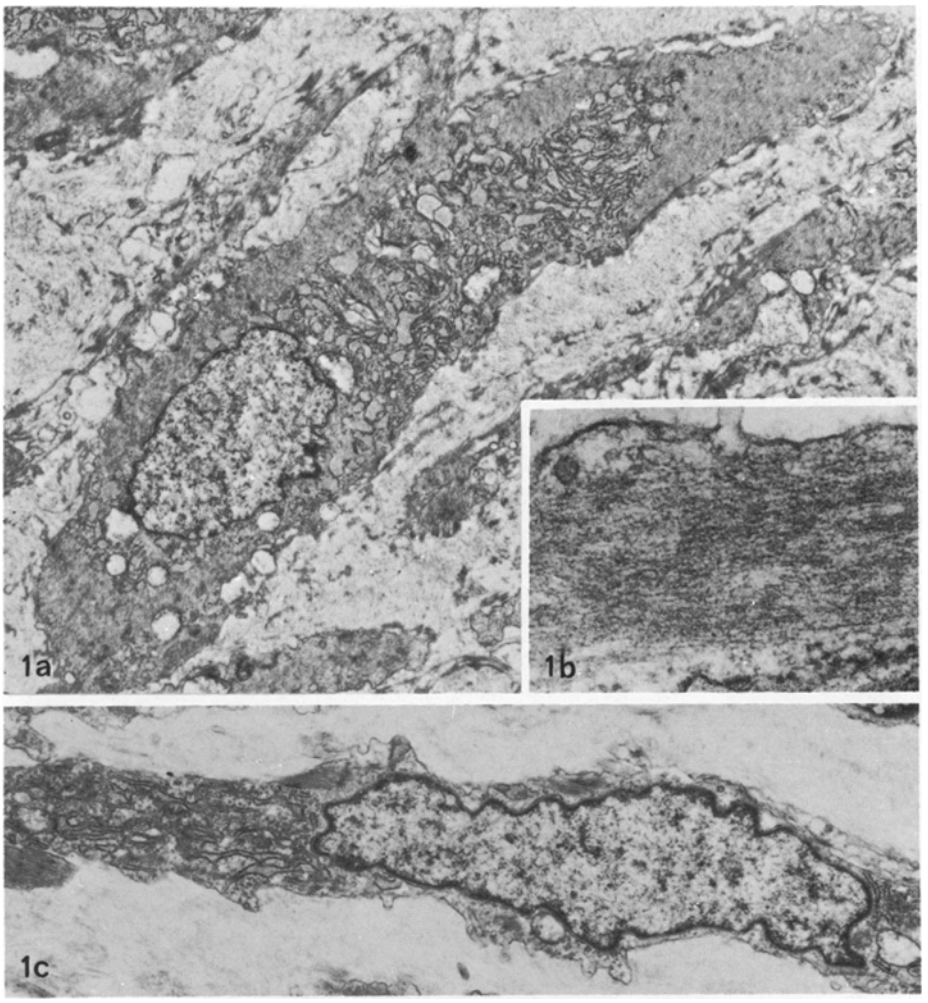


**Fig. 1.a** A myofibroblast with abundant microfilaments in invasive ductal carcinoma. ×5,800. **b** Detailed structures of a bundle of microfilaments of another myofibroblast. ×57,000. **c** A myofibroblast with less abundant microfilaments in invasive ductal carcinoma. ×7,400

of microfilaments closely resembled in structure the "myofibroblasts" described by Majno et al. (1971) and Gabbiani et al. (1972). Thus, a continuous cell-spectrum from the fibroblast at one end to the myofibroblast at the other was clearly noted in our material. In this paper, we use the term "myofibroblast" for a cell that shows the characteristics of fibroblasts and also possesses a variable quantity of microfilament bundles (Fig. 1 a, b, c).

A discontinuous external lamina covered the surface of some myofibroblasts. Cytoplasmic caveolae were scanty. Microtubules were present in most myofibroblasts. Myofibroblasts were connected with one another by three kinds of junctions; atypical desmosomes types 1 and 2, tentatively named by us in this paper,

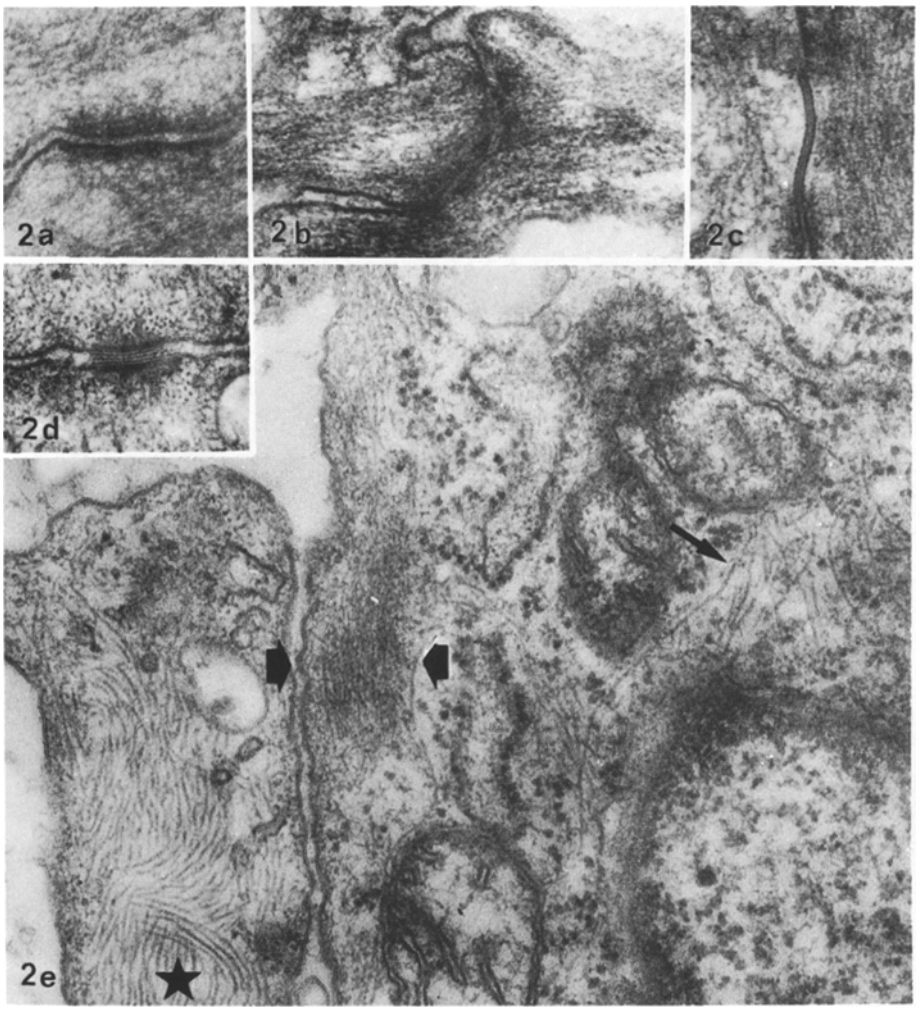


**Fig 2. a** An atypical desmosome, type 1, between myofibroblasts. × 57,000. **b** An atypical desmosome, type 2, between myofibroblasts. × 57,000. **c** A gap junction between myofibroblasts. × 57,000. **d** A typical desmosome between epithelial cells of fibroadenoma. × 57,000. **e** A portion of a myofibroblast in intraductal carcinoma. *Thick arrows:* a bundle of microfilaments. *Thin arrow:* intermediate filaments. *Asterisk:* an area filled with intermediate filaments, probably a small part of a myofibroblast. × 57,000

and gap junctions (Fig. 2a, b, c). As compared with typical desmosomes (Figs. 2d, 3c) the atypical desmosomes type 1 did not form definite attachment plaques but the cytoplasmic surface of their cell membrane was lined with an amorphous substance of moderate density. Insertion of filaments into this amorphous substance was usually indistinct. Between the apposed cell membranes an electron dense central line was usually formed. However, this line was less clear than that seen in typical desmosomes. The atypical desmosomes

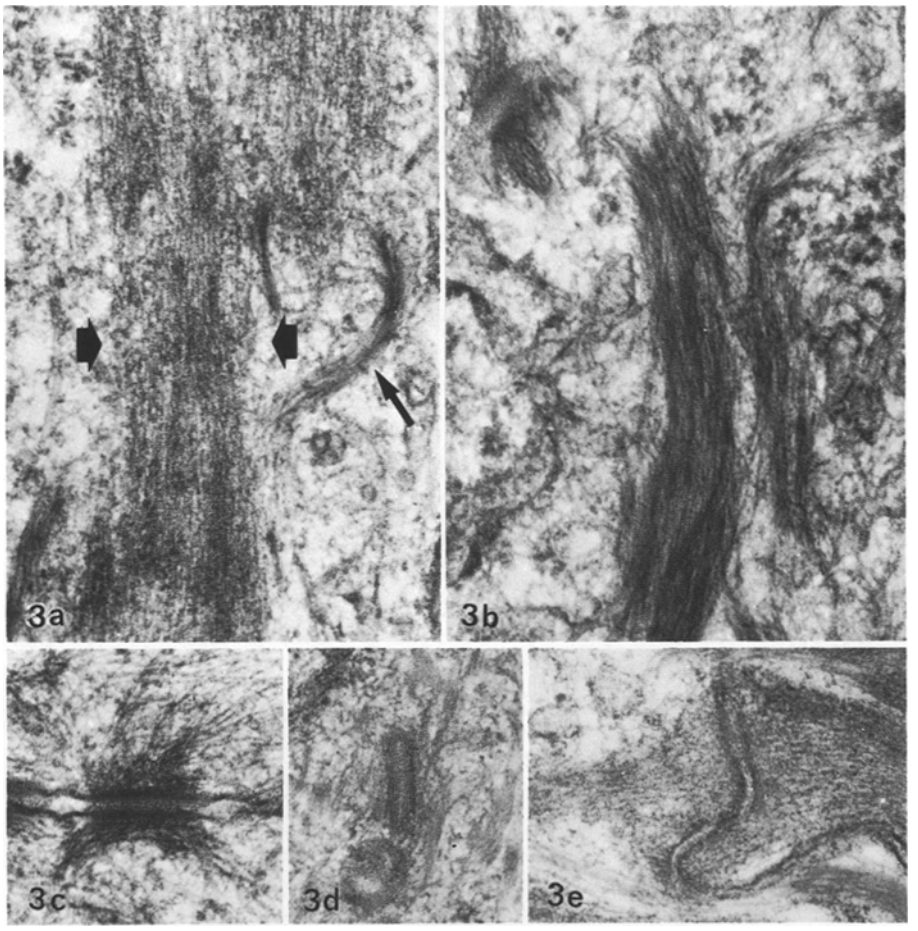


**Fig. 3. a** A part of a myoepithelial cell in invasive ductal carcinoma. *Thick arrows:* A bundle of microfilaments. *Thin arrow:* dense bundles of tonofilaments. × 57,000. **b** Dense bundles of tonofilaments and an intracytoplasmic desmosome (*left above*) in the same myoepithelial cell as that in Fig. 8. × 57,000. **c** A typical desmosome between a myoepithelial cell (*below*) and a carcinoma cell (*above*) in invasive ductal carcinoma. × 57,000. **d** An intracytoplasmic desmosome in a myoepithelial cell in invasive ductal carcinoma. × 57,000. **e** An atypical desmosome, type 2, between myoepithelial cells in invasive ductal carcinoma. × 57,000

type 2 resembled intermediate junction and fascia adherens of cardiac muscle in that the bundles of microfilaments terminated at these junctions. These desmosomes were similar in structure to "70F-maculae adherentes" described by McNutt and Weinstein (1973).

The myofibroblasts and a few macrophages were sometimes contiguous with carcinoma cells, but no intercellular junctions were formed between myofibroblasts and carcinoma cells.

In intraductal papillomatosis and intraductal carcinoma, the arrangement of myofibroblasts which encircled the tumor ducts corresponded to that of the delimiting fibroblasts (Ozzello, 1970) of the normal breasts.

So-called intermediate filaments, 80–100 Å in diameter, differing from tonofilaments by their dispersed arrangement, were occasionally evident in myofibroblasts, although not conspicuous in most of them. They were not arranged into bundles (Fig. 2e).

Myofibroblasts did not show cellular polarity.

*Myoepithelial Cells*

Our observations of myoepithelial cells in the normal breast tissue agree with previous descriptions (Murad, 1968; Schäfer, 1969; Tannenbaum, 1969; Ozzello, 1971; Stirling, 1976).

Myoepithelial cells were detected in 1 case each of intraductal papillomatosis and intraductal carcinoma, and also in 3 of 10 invasive ductal carcinomas. The ultrastructural characteristics of myoepithelial cells in the cancerous tissue were summarized as follows:

(1) They contained bundles of microfilaments, 50–70 Å in diameter, which were usually more abundant than in the normal control tissue (Fig. 3a). Dense bodies were formed in these bundles.

(2) Dense bundles of tonofilaments, 80–100 Å in diameter, were seen in the cytoplasm (Fig. 3b). Occasionally tonofilaments were intermingled with microfilaments but were distinguished from the latter by their arrangement and diameter.

(3) The cells were connected to adjacent carcinoma cells or myoepithelial cells by typical desmosomes which had attachment plaques and an intercellular dense line (Figs. 3c, 7b, 10). Tonofilaments converged on these junctions.

Features (2) and (3) were specific to the myoepithelial cells, but not found in the myofibroblasts. Dense bundles of tonofilaments were inconspicuous in the control myoepithelial cells. Myoepithelial cells in breast carcinoma showed some anaplastic features; the basal lamina was discontinuous or had almost disappeared, and cellular polarity was usually obscure or sometimes nearly lost. Hemidesmosomes, which were present on the basal plasma membrane of the normal myoepithelial cells, were hardly observable in most cases but the myoepithelial cells in intraductal carcinoma had some of these structures. Intracytoplasmic desmosomes were found in some of the myoepithelial cells (Fig. 3b, d). The amount of rough endoplasmic reticulum varied but was never large. This organelle was usually less abundant in the myoepithelial cells than in the myofibroblasts. In addition to the typical desmosomes, the myoepithelial cells in breast carcinoma frequently formed atypical desmosome type 2 (Fig. 3e) as noted between myofibroblasts.

In intraductal papillomatosis and intraductal carcinoma, myoepithelial cells were arranged in a single layer at the periphery of the ductal structures composed of tumor cells (Fig. 4). They were characterized by the previously mentioned features. Although the arrangement of myoepithelial cells was somewhat

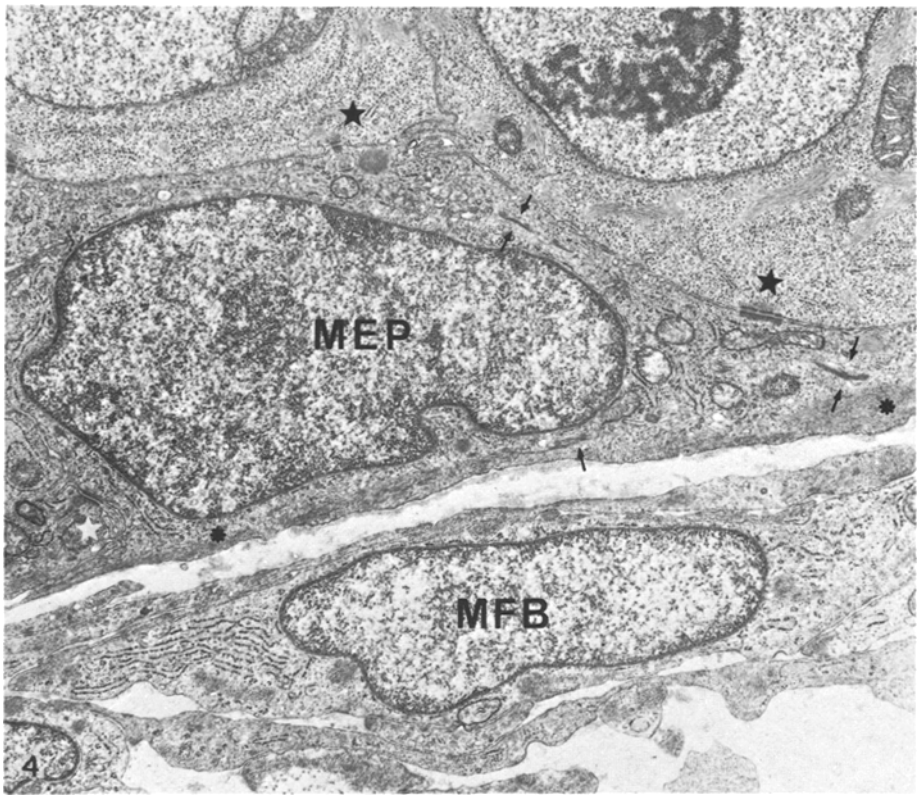


**Fig. 4.** A myoepithelial cell (*MEP*) and myofibroblast (*MFB*) in intraductal papillomatosis. *Black asterisks:* typical desmosomes between a myoepithelial cell and tumor cells. *White asterisk:* a typical desmosome between adjacent myoepithelial cell. *Small arrows:* dense bundles of tonofilaments. * marks: bundles of microfilaments. Note well preserved cellular polarity of the myoepithelial cell in this case. × 13,000

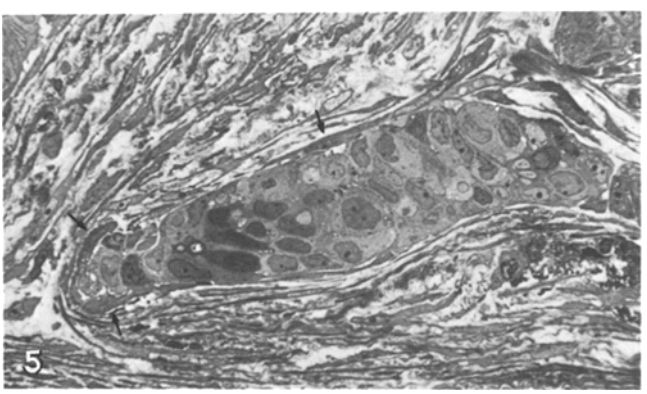


**Fig. 5.** A semi-thin section of carcinoma cell nest stained with toluidine-blue. Myoepithelial cells (*arrows*) are located at the periphery (invasive ductal carcinoma). × 1,200

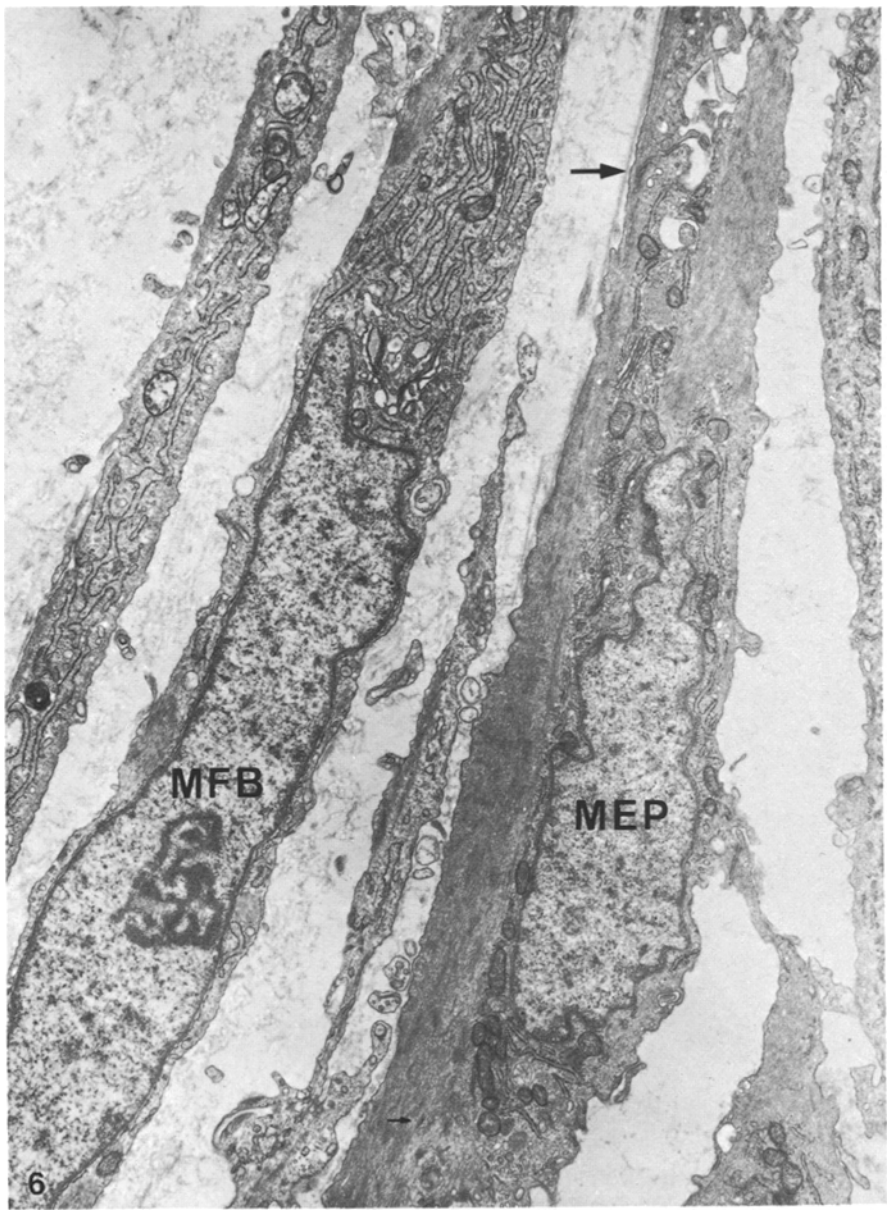


**Fig. 6.** Myoepithelial cells (*MEP*) at the periphery of a carcinomatous duct-like structure and myofibroblasts (*MFB*) with less abundant microfilaments (invasive ductal carcinoma). *Large arrow:* an atypical desmosome, type 2. *Small arrow:* dense bundle of tonofilaments. × 11,000

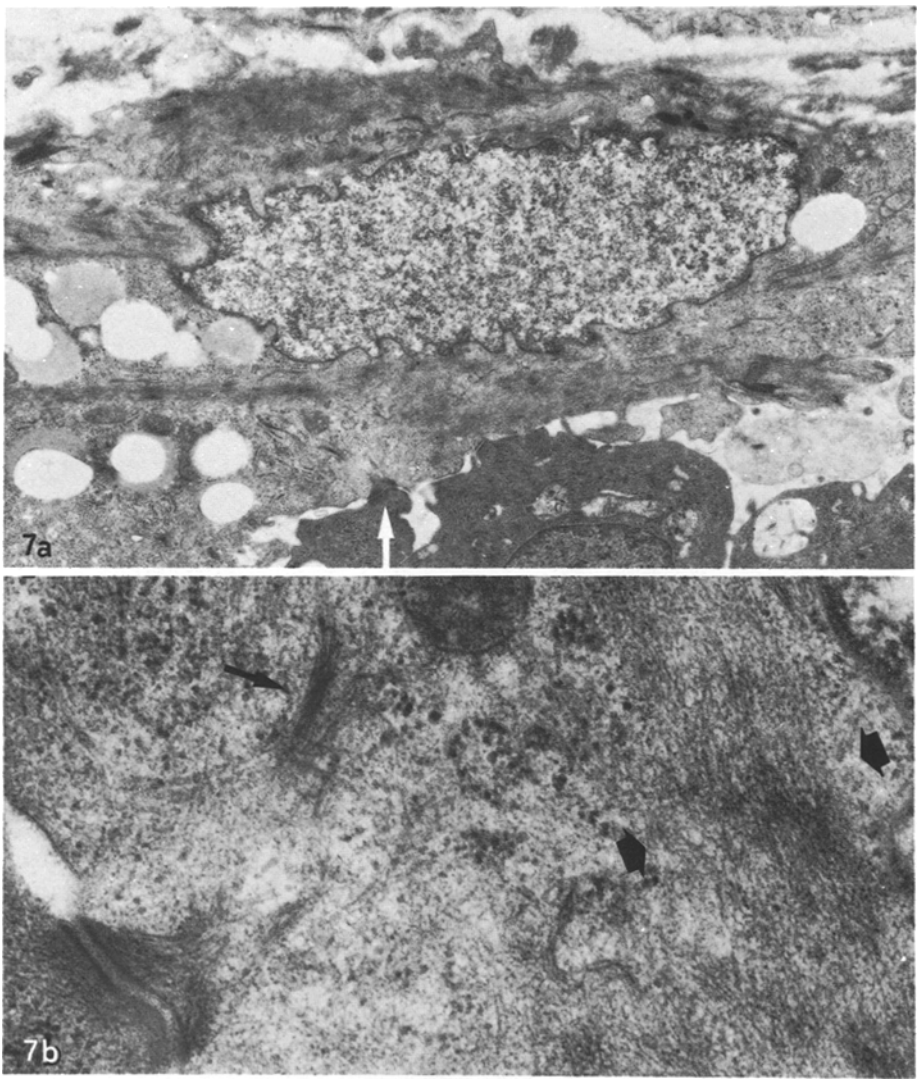


**Fig. 7. a** An isolated myoepithelial cell attached to a carcinoma cell by a typical desmosome (a white arrow) in invasive ductal carcinoma. Note obscure polarity of this cell. ×8,100. **b** Detailed structures of the desmosome in Fig. 7a, dense bundles of tonofilaments (*thin arrow*) and bundles of microfilaments (*thick arrows*). ×47,000

distorted in the intraductal carcinoma, their polarity was generally preserved in these cases. Distinction between myoepithelial cells and myofibroblasts was easy, from their location.

In invasive ductal carcinoma, myoepithelial cells were detected at the periphery of some carcinomatous duct-like structures and carcinomatous cell nests, but were not seen centrally (Fig. 5). They were arranged in a single layer, or dispersed around carcinoma cells, but most neoplastic cell clusters lacked

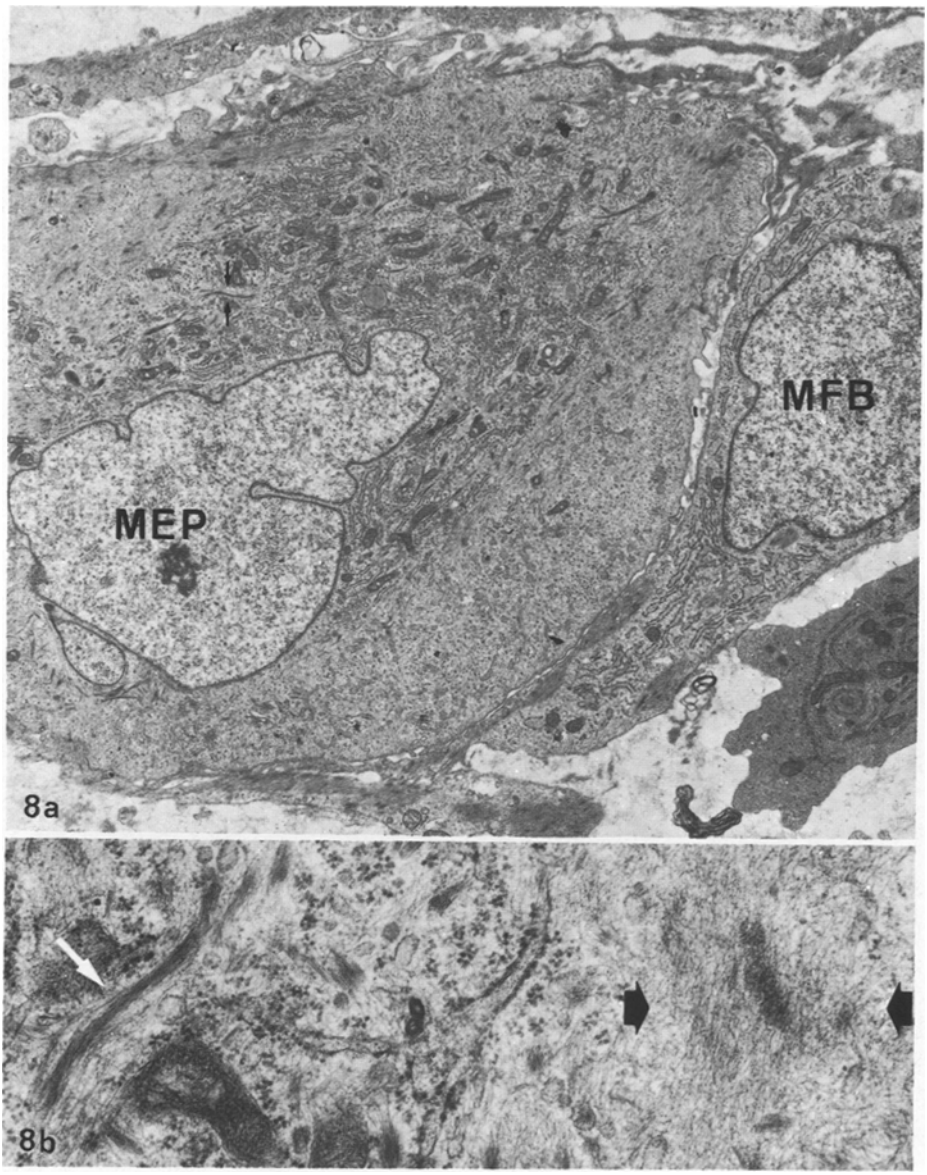


**Fig. 8. a** A myoepithelial cell (*MEP*) and contiguously located myofibroblast (*MFB*) in invasive ductal carcinoma. No desmosomes are observed in this myoepithelial cell. ×5,400. **b** Detailed structures of the myoepithelial cell in Fig. 8 a. *White arrow:* dense bundles of tonofilaments (as indicated by small arrows in Fig. 8 a). *Thick arrows:* bundles of microfilaments with dense bodies. ×32,000

myoepithelial cells. Myoepithelial cells in invasive ductal carcinoma were apparently very few compared with carcinoma cells and myofibroblasts in the stroma. A myoepithelial cell at the periphery of carcinomatous duct-like structure is shown with a myofibroblast in the stroma in Fig. 6 where the ultrastructural characteristics of the two types of cell can be clearly noted.

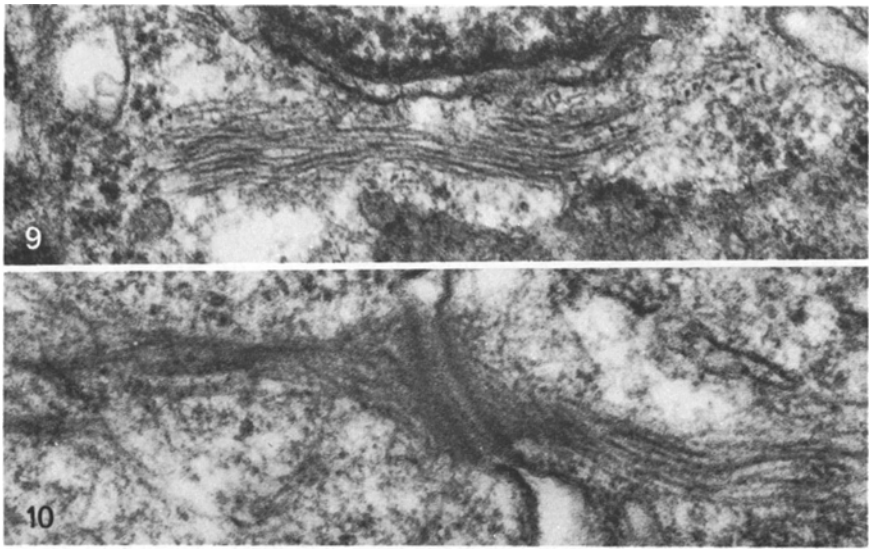


**Fig. 9.** A bundle of tonofilaments in a carcinoma cell in invasive ductal carcinoma. × 57,000

**Fig. 10.** A typical desmosome between a myoepithelial cell (*left*) and a carcinoma cell (*right*). × 82,000

This myoepithelial cell had a discontinuous basal lamina, preserving cellular polarity.

An isolated myoepithelial cell (shown in Fig. 7a, b) was from a case of invasive ductal carcinoma. This cell was an example of the most highly anaplastic myoepithelial cells in the present material. It contained bundles of microfilaments, dense bodies and dense bundles of tonofilaments. Some of the latter filaments were inserted into attachment plaques of desmosomes. In the cytoplasm there was a scanty rough endoplasmic reticulum and rather abundant free ribosomes. No evident basal lamina was found. The cellular polarity was very obscure.

A cell with bundles of microfilaments in Fig. 8a, b from another case of invasive ductal carcinoma, was defined as a myoepithelial cell owing to the presence of dense bundles of tonofilaments, in spite of the lack of typical desmosomes. This cell had rather abundant rough endoplasmic reticulum. Microfilaments were not always situated beneath the plasma membrane nor were they always found running along the long axis of the cell.

### *Tonofilaments in Myoepithelial Cells and Carcinoma Cells*

Breast carcinoma cells, including tumor cells in intraductal papillomatosis, had a variable amount of bundles of tonofilaments 80–100 Å in diameter (Fig. 9). Some tonofilaments were connected with attachment plaques of typical desmosomes and they were usually arranged more loosely than those in the myoepithelial cells. As a consequence, desmosomes between carcinoma cells and myoepithelial cells were frequently asymmetrical in the arrangement of tonofilaments

(Fig. 10). Bundles of tonofilaments on the myoepithelial cell side were denser than those on the carcinoma cell side. This asymmetry was also observed in desmosomes between tumor cells and myoepithelial cells in intraductal papillomatosis (Fig. 4, black asterisks).

## Discussion

### *Myofibroblasts*

Ordinary Fibroblasts in a resting phase have poorly developed rough endoplasmic reticulum and other cell organelles (Bloom and Fawcett, 1975). Delimiting fibroblasts in the normal mammary gland show the same features (Ozzello, 1970). In our study, most stromal cells in breast carcinoma had an abundance of rough endoplasmic reticulum and other cell organelles, showing the characteristic features of activated fibroblasts; and at the same time, most of them contained bundles of microfilaments, just like smooth muscle cells. If we assume that the ordinary fibroblasts contain no bundles of microfilaments as stated by Bhawan et al. (1979), most of the stromal cells in our material belonged to a cell category other than fibroblasts, because of the presence of bundles of microfilaments, in variable quantity. Fibroblasts without microfilaments were few. Probably the name myofibroblast proposed by Majno et al. (1971) is most suitable for these cells.

However, it must be taken into consideration that microfilaments of the actin type are not structures specific to muscle, but are found in a wide variety of cells (as reviewed by Wessells et al., 1971 and Clarke and Spudich, 1977). The distribution pattern of bundles of microfilaments in cultured cells (Goldman, 1975) resembles that in myofibroblasts. Although the environment of culture media differs significantly from that of the stroma of a carcinoma, it is not surprising that these microfilaments occur in the fibroblasts in vivo.

Smooth muscle cells are known to produce collagen and elastic fibers in vivo and in vitro (Ross, 1971 a, b). As seen in his micrographs, smooth muscle cells producing connective tissue protein in vitro possess many dilated cisternae of rough endoplasmic reticulum in their axial cytoplasm, and bundles of microfilaments with dense bodies in their periperal cytoplasm. Thus these cells show electron micrographic features similar to those of myofibroblasts in our materials. McLean et al. (1979) reported that smooth muscle cells in the monolayer culture stopped contracting after lwk. Their photographs also demonstrate cells quite resembling our myofibroblasts.

All these facts suggest that the fibroblasts and some, if not all, smooth muscle cells belong to the same cell system, and that myofibroblasts represent an intermediate type between the two cell types. Both fibroblasts and smooth muscle cells may present features of myofibroblasts under certain conditions.

The myofibroblasts have few types of intercellular junctions (Gabbiani et al., 1972; Gabbiani and Majno, 1972; Ryan et al., 1973, 1974; Wirman 1976; Vasudev, 1978). The present observations revealed that these are atypical desmosomes, type 1, type 2 and gap junctions. No typical desmosomes are formed.

*Myoepithelial Cells*

Both the myoepithelial cells and the myofibroblasts have bundles of microfilaments and associated dense bodies. However, dense bundles of tonofilaments and typical desmosomes are characteristic structures of myoepithelial cells and never occur in the myofibroblasts.

Dense bundles of tonofilaments in the myoepithelial cells and in some of the carcinoma cells, suggested squamous metaplasia, though no keratohyalin granules were observed. The same type of tonofilaments were described in myoepithelial cells in sclerosing adenosis and cysts (Murad, 1968).

It is well known that intraductal carcinoma has a single layer of myoepithelial cells arranged continuously or discontinuously at the periphery of carcinomatous ducts (Goldenberg et al., 1969; Ahmed, 1974; Gould, 1975). Ahmed (1978) and Ozzello (1971) thought that they were not malignant.

Ozzello (1971) and Fisher (1976) reported that human invasive duct carcinoma did not contain myoepithelial cells. Hamperl (1970) in a light microscopic study, and Sykes (1968) in an ultrastructural study, reported that myoepithelial cells were located in the periphery of carcinoma cell nests. But they did not make it clear whether these myoepithelial cells were neoplastic or residual. Our findings of cellular anaplasia in myoepithelial cells do not fully support the view of their neoplastic origin, because residual myoepithelial cells in the pre-existing ducts involved by carcinoma may also show some kinds of cellular "anaplasia". A different approach will be required to solve this problem.

*Relationship Between Myoepithelial Cells and Myofibroblasts*

Ahmed (1974) suggested the possibility that myoepithelial cells might be transformed into fibroblasts. He also suggested in his monograph (1978) that myofibroblasts in the stroma might be derived from myoepithelial cells. This is an important hypothesis, suggesting transformation of epithelial cells to non-epithelial cells. If this transformation occurs in the breast intermediate cell types should be observed.

In breast carcinoma myofibroblasts were occasionally located next carcinoma cells. This location is similar to that of myoepithelial cells, but we could not find any kind of intercellular junctions between carcinoma cells and myofibroblasts in any case of breast carcinoma. No bundles of tonofilaments were observed in any areas of cytoplasm of the myofibroblasts. Thus, we could not detect any characteristics of epithelial cells in the myofibroblasts.

Cells which contained bundles of microfilaments and were connected with adjacent cells by typical desmosomes always had bundles of tonofilaments and were thus regarded as myoepithelial cells. Bundles of tonofilaments were thought to be characteristic of the epithelial cell.

These observations suggest that the myoepithelial cells are a cell entity distinct from myofibroblasts. We speculate that the myoepithelial cells in breast carcinoma are epithelial in origin, while myofibroblasts are derived from fibroblasts under certain pathological conditions. The close relationship between carcinoma

cells and myofibroblasts and macrophages may be a manifestation of tissue reaction to carcinoma growth.

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