ULTRASTRUCTURAL CHARACTERISTICS OF PARENCHYMATOUS CELLS IN BREAST CANCER

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Ultrastructural features of parenchymatous cells in breast cancer have been the subject of much study [1, 2, 4-6]. However, many problems in the histogenesis of breast cancer, including the degree of preservation or loss of organ specificity by the tumor cells, still remain highly contradictory.

The object of this investigation was an electron-microscopic study of the morphology of parenchymatous cells of lobular breast cancer, for the purpose of detecting tumor cells of different types and with different directions of differentiation, to establish the characteristic ultrastructural features of each of them, and on that basis to determine the histogenesis of the carcinoma.

Accordingly a comparative study was made of the submicroscopic features of cells from lobules of unchanged breast tissue and parenchymatous cells from infiltrative carcinoma of this organ.

EXPERIMENTAL METHOD

Unchanged breast tissue was studied in six cases and lobular forms of carcinoma in nine cases. Material for electron-microscopic investigation was prepared in the usual way [3]. Preparations were studied and photographed in the JEM-100C electron microscope.

EXPERIMENTAL RESULTS

Epithelial cells lining the intralobular ducts of the normal mammary gland have large, basal nuclei of oval or circular shape, characterized by a homogeneous or, in some cases zonal distribution of chromatin.

Secretory granules with lipid and protein contents, of varied electron density, can be seen in the apical part of the cytoplasm of the epithelial cells. Casein inclusions are frequently observed (Fig. 1). Organelles and intracellular tubules also are present in some cells. The plasma membranes of adjacent cells are firmly united with each other in places and connected by desmosomes or contacts of locking type. The apical plasmalemma of these cells forms numerous microvilli of varied width and height.

The myoephithelial cells are osmiophilic, and this is responsible for their dark appearance (Fig. 1). A feature of the nuclei of the myoepithelial cells is their definite polymorphism: oval, round, and rectangular nuclei can be seen, sometimes with well defined invaginations. The cytoplasm of these cells contains many free ribosomes and polysomes, arranged in no special order throughout the cytoplasm. A characteristic feature of the myoepithelial cells is that they contain fibrillary material, lying both between the nucleus and the basement membrane and also in the lateral parts of the cytoplasm. Most cells have micropinocytotic vesicles in their apical and basal parts. Communication between the basement membrane and myoepithelial cells is by means of hemidesmosomes.

Both epithelial and myoepithelial cells may be dark or pale depending on their functional state. The number and degree of differentiation of these cells vary considerably.

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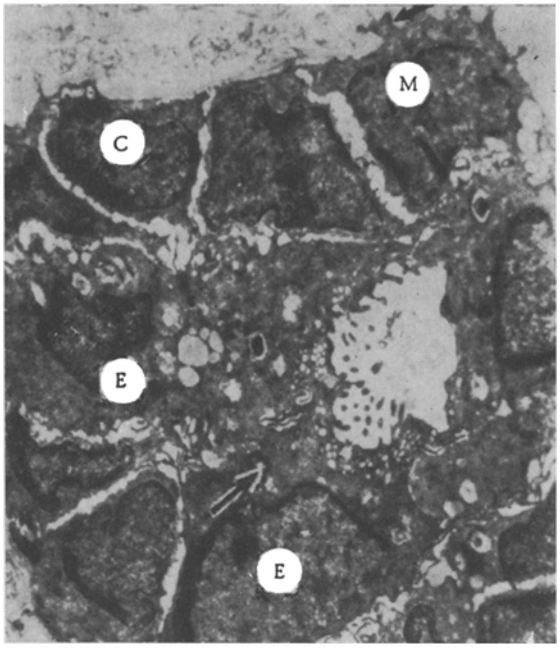

Fig. 1. Intralobular duct of unchanged breast tissue. E) Cytoplasm of epithelial cells. Lipid, protein, and casein granules (arrow) are visible; M) invagination of nuclear membrane, concentration of pinocytotic vesicles in cytoplasm; C) cambial cell. Nucleus occupies a large part of cell cytoplasm, which surrounds it in a narrow rim.

Besides the cells described above, others differing in many respects both from the secretory epithelium and the myoepithelium, also were found in the lobules. Usually these were small cells with a large oval rectangular nucleus, occupying a considerable part of the cell. Chromatin was present in the nucleus in the form of clumps, mainly marginal in distribution.

The poorly developed cytoplasm forms a narrow rim. It is homogeneous, of average electron density, and contains many free ribosomes and polysomes. Cells of this type are few in number and, as a rule, they lie directly on the basement membrane (Fig. 1). They are undifferentiated and must be classed as cambial cells of the breast. It can be postulated that these are cells with high potential for division which, under certain conditions, mature and acquire the specific features of either myoepithelium or secretory epithelium.

Consequently, the epithelium of the lobules consists of cells of three types: secretory, myoepithelial, and cambial. Eash of them is characterized by definite electron-microscopic features, so that they can be clearly differentiated from one another.

Ultrastructural investigation of breast cancer of lobular origin also revealed three types of cells among the parenchymatous cells of the tumor.

Cancer cells of type I are relatively large. Their nuclei are more often hypertrophied, circular or oval in shape, and frequently have many invaginations. Chromatin is unevenly distributed in clumps among the karyoplasm and concentrated mainly near the nuclear membrane. Granules of specific secretion appear in the cytoplasm of individual cells. Usually they are single, but in the most highly differentiated cells their number is appreciably increased. They are accompanied by casein inclusions. In some cells lipid granules almost completely fill the cytoplasm (Fig. 2). Intracellular tubules are visble in individual cells. Cytoplasmic outgrowths, projecting into the lumen of these tubules, are short and sometimes the lumen of the tubules is filled with products of cell disintegration. Numerous filamentous structures may be seen, but their numbers vary within wide limits. Filamentous bundles of varied thickness are located in the immediate vicinity of the nucleus and often run parallel to the nuclear membrane (Fig. 3).

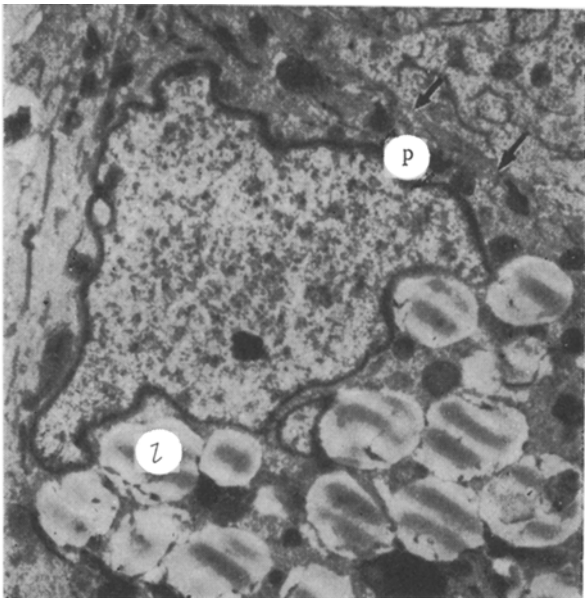

Fig. 2. Cancer cell of epithelial type. Cytoplasm contains many lipid inclusions (*l*) and protein granules (p). Contact between two neighboring cells by simple contact between plasma membranes indicated by arrows.

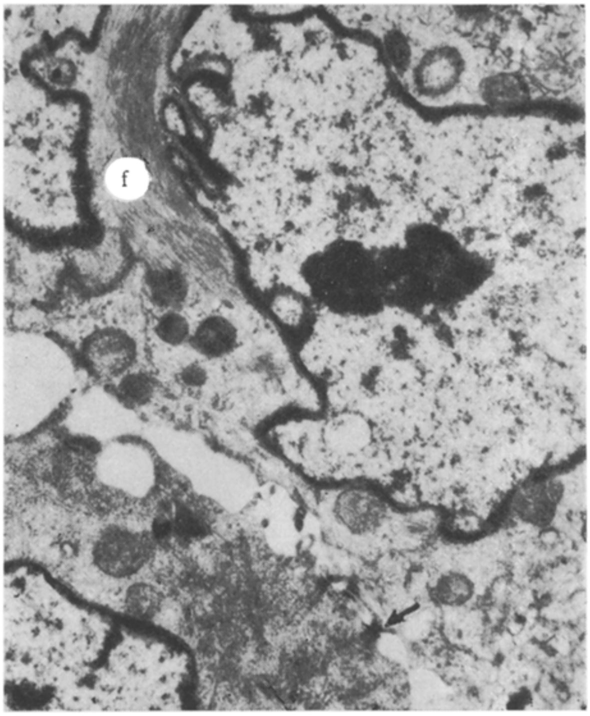

Fig. 3. Cancer cell of epithelial type. Invagination of nucleus, filamentous bundles (f) visible in cell cytoplasm. Contacts between neighboring cells effected through desmosomes (arrow).

The plasmalemma of some tumor cells in folded, intercellular contacts are infrequent, and most of them consist of simple contact between the two plasmalemmas, although sometimes desmosomes also are present. Single microvilli of different sizes and shapes may be seen on the apical surface of these cancer cells, but they are not oriented in a definite direction.

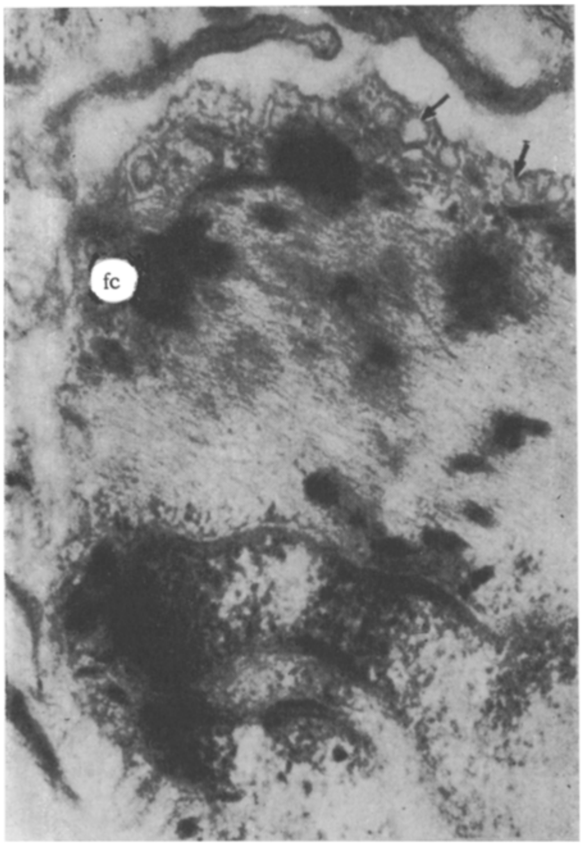

Fig. 4. Cancer cell of myoepithelial type. Part of invaginated nucleus can be seen, large concentration of fibrils with focal condensations (fc) present in cytoplasm, numerous pinocytotic vesicles (arrows) at periphery of cell.

The parenchymatous cells of type I, although characterized by certain features common to all cancer cells, nevertheless reveal distinct ultrastructural features (filaments, microvilli, desmosomes, secretory granules) of the secretory epithelium of the normal breast.

Cancer cells of type II are mainly comparatively small and polygonal in shape. Most of the cell is occupied by a rectangular nucleus, whose nucleolemma often creates deep invaginations. The poorly developed cytoplasm of average electron density is filled with fibrillary material, most frequently in the form of bundles of varied thickness, not oriented in any particular direction (Fig. 4).

A particularly characteristic feature of cells of this type is the presence of numerous micropinocytotic vesicles. In some cells focal concentration of vesicles can be seen in the peripheral regions of the cytoplasm giving it a honeycombed appearance. Cancer cells of this type reveal the presence of structures which are characteristic of normal myoepithelial cells (the presence of fibrillary material, pinocytotic vesicles, etc.).

In each of the groups described above cells can be seen with different degrees of differentiation and functional maturity; their relative numbers vary not only from case to case, but also in the same tumor.

Cells largely similar to the undifferentiated cells described above, i.e. to the cambial cells of the normal lobule, also could be seen in all the preparations examined; for that reason, in the writer's opinion they should be classed as undifferentiated breast cancer cells.

It can thus be concluded on the basis of this description that breast cancer of lobular origin can vary in its cellular composition. Cells with ultrastructural features characteristic of the three types of principal cells encountered in unchanged breast tissue may be present in it (secretory epithelium, myoepithelium, and cambial cells). In their ultrastructure, parenchymatous cells of lobular carcinoma, like cells of the normal lobule, are at different levels of differentiation and in different phases of functional state.

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EFFECT OF THYMIC AND PINEAL POLYPEPTIDE FACTORS ON RADIATION CARCINOGENESIS

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During tumor growth *in vivo* the reactions of cellular immunity and functional activity of T lymphocytes are depressed [11, 13]. If the disturbed function of the T lymphocytes is restored by means of certain drugs such as levamisole, phenformin, or epithalamin in some cases growth of both spontaneous tumors and tumors induced by chemical carcinogens is inhibited [2, 7, 8, 12]. Data showing the important role of the thymus in regulation of T lymphocyte function and in antitumor immunity [11, 13] indicate the urgent importance of a study of the effect of the active factors (hormones) of the thymus on the development and growth of neoplasms.

The object of this investigation was to study the effect of a polypeptide thymic factor (thymarin), which specifically restores disturbed T lymphocyte function and reactions of cullular immunity [10], and also of pineal polypeptide factor (epithalamin), whose stimulating effect on immunity is evidently realized through its varied influence on the neuroendocrine system [4], on radiation carcinogenesis.

EXPERIMENTAL METHOD

Experiments were carried out on 148 noninbred female albino rats bred at the Research Institute of Radiation Hygiene, Ministry of Health of the RSFSR, aged 3 months, and subjected to whole-body x-ray irradiation in a single dose of 4 Gy (400 rads, RUM-17 apparatus, voltage 200 kV, current 15 mA, filters 0.5 mm Cu + 1 mm Al, focus distrance 50 cm, exposure dose rate $0.23 \cdot 10^{-3}$ A/kg (54 R/min). The animals were divided into three groups. Starting from the third week after irradiation they received 10-day courses, once a month throughout life, of 0.2 mg thymarin [10] or epithalamin [8] in 0.2 ml 0.9% NaCl solution, or the same volume of solvent (control) subcutaneously. Animals which died were autopsied and all neoplasms discovered were studied under the microscope. Student's t test and P criterion were used in the statistical analysis of the results [14]. Single wholebody irradiation of the rats in a dose of 4 Gr led in these experiments to the development of tumors in 74.1% of animals that survived until discovery of the first tumor. Administration of epithalamin had a distinct inhibitory effect on radiation carcinogensis: the frequency of appearance both of all tumors and of only malignant tumors was reduced (by 1.3 and 2.7 times respectively). The effect of the thymic factor was a little weaker than the effect of the pineal factor, and was expressed as a reduction in the frequency of malignant neoplams by 1.9 times, whereas the total frequency of tumor development showed no significant change compared with the control (Table 1; Fig. 1).

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