Electron Microscopy of the Human Endometrial Carcinoma*

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SUMMARY

The cancer cells were arranged in membranes or formed globelike groups. The shape of the cells varied from columnar to squamous. The apical cell surface was irregular or possessed microvilli, but no correlation of this appearance to some consistent feature of the cytoplasm was observed. The basal cell surface of some squamous cells made deep projections into the connective tissue. This was interpreted as a sign of reduced contact inhibition. Sometimes a row of cancer cells lacked the basement membrane. These cells had a zone of ground substance, with a high density at the basal cell surface. The A cells of the adenocarcinomas contained both an increased number of free ribonucleoprotein particles and a cytoplasmic ground substance of higher density than the B cells.

The cell organelles had mainly a normal ultrastructure but varied in number. However, some mitochondria were large and contained fewer cristae than normal. Several types of cell inclusion were observed. No cellular component or virus-like particle that might be specific for this type of cancer cell was observed.

The interphasic cancer cells of the glandular epithelium in the uterine body of man have a varying structure as seen under the light microscope. In general, the cell is characterized by a large, irregular nucleus with hypertrophic nucleoli and a cytoplasm showing signs of dedifferentiation. With regard to the amount of nucleic acid, it is sometimes possible to classify the cancer cells into type A and type B cells (4).

A further knowledge of several of the cellular components in the cancer cell requires the higher resolution of the electron microscope. Results of electron microscopy of the normal endometrium have been published by several authors (1–3, 5–7, 9–12, 15–21), but the reports on the endometrial carcinoma still are few (16, 17). The present paper will add some information on the ultrastructure of the different types of cancer cell which are observed in adenocarcinomas of the uterine body.

MATERIALS AND METHODS

The specimens of the endometrial carcinomas were obtained during diagnostic curettage from four women, one being in the late secretory phase of the menstrual cycle and three in the menopause.

For electron microscopy a small piece of the mucosa of the uterine wall was removed with a biopsy curette and immediately placed in a buffered 1 per cent solution of osmium tetroxide. After dehydration in ethyl alcohol, the specimens were embedded in butyl methacrylate. The sections were made on an ultramicrotome designed by Sjöstrand and examined in an RCA EMU-2C microscope.

RESULTS

Light microscopy.—Light microscopy revealed adenocarcinoma of high or moderate differentiation in all the cases.

Electron microscopy.—The epithelial cells of the adenocarcinoma in the uterus varied from tall columnar cells to low squamous cells. Sometimes the cancer cells did not form epithelial membranes but were arranged in globelike groups. These cells were polygonal. Some cancer cells showed a higher electron density than did the surrounding cells (Figs. 1, 6). The higher density of the cytoplasm was caused by an increased number of free-lying ribonucleoprotein (RNP) particles and by a higher density of the ground substance of the cell.

The apical cell surface in the epithelial membranes either had an irregular course (Fig. 3) or was specialized into microvilli (Figs. 1, 2, 4, 5), but the cell surface of the groups of polygonal

* This work was supported by a grant from "Riksföreningen mot cancer," Stockholm, Sweden.
cells was always irregular (Figs. 6, 9). The basal cell surface in the epithelial membranes generally was slightly irregular (Fig. 8). However, the low squamous type of cell showed several deep projections into the connective tissue (Fig. 4). The basal cell membrane generally adhered to a basement membrane, but sometimes a cluster of cells was lying freely among the connective tissue cells. A zone of the cytoplasm at the basal cell surface of these cells showed a dense ground substance, which lacked most of the other cell components (Fig. 8).

The mitochondria were observed to vary in number in the different cells. The structure of most of the mitochondria was similar to that of the mitochondria of a normal glandular epithelium, but some large mitochondria had cristae lying more apart than is normal (Fig. 3).

The Golgi apparatus was visible in the upper part of the cell. The ultrastructure of the different Golgi components was similar to that of these components in a normal uterine gland cell.

The rough-surfaced membranes were present in varying numbers. Sometimes a group of these membranes was noticed in the vicinity of the nuclear membrane (Fig. 5). The number of freely lying RNP particles varied in the different cells.

Some inclusions of the cytoplasm were lipide globules, small and large vesicles, granules, and lamellated bodies. The large vesicles and the granules have not yet been observed in normal uterine epithelium.

Lipide globules were frequent in some cells; they were noticed as areas with an irregular outline (Figs. 6, 7, 10, 11). A few of them contained vacuoles, a dense substance, or groups of parallel membranes.

Vesicles of two types were observed. One type of vesicle had a maximum size of 0.5 μ. These vesicles were surrounded by a single membrane, and some vesicles contained an irregularly distributed substance (Figs. 2, 5–7, 9–11). The other type of vesicle was larger, with a maximum size of 2 μ. It was bounded by a varying number of membranes, and it usually contained membranes which ran irregularly in a diffusely scattered substance (Figs. 9–11).

Granules of a varying ultrastructure were present in some cells (Figs. 2, 9). They were most frequent in the apical parts of the cells. The granules had a maximum size of about 1 μ. A single membrane surrounded some granules. The interior of the granules was composed of a dense, granulated substance with areas of vacuoles, membranes, and dark structures.

Lamellated bodies with a maximum size of 2 μ were observed in different parts of the cells (Figs. 7, 10). They were surrounded by many parallel membranes and contained a dense substance.

**DISCUSSION**

The microscopic diagnosis of endometrial adenocarcinoma sometimes is difficult due to the similarity in appearance between some endometrial hyperplasia and adenocarcinoma (8, 18). Furthermore, the altered surroundings of the normal epithelium in a cancerous uterus might change the structure of the normal cells to render a classification difficult. It cannot always be stated, therefore, that a certain epithelial cell of a biopsy really is a cancer cell. In the present material the described cells are probably all malignant, but this cannot be proved. However, with this reservation in mind they have been called cancer cells.

Several cells of the uterine adenocarcinoma had an ultrastructure that was different from that of the normal glandular epithelium. The differences were evident in the general shape of the cells and in the morphology of the intracellular structures.

The outline of the cells in the adenocarcinoma varied with respect to both the apical and the basal cell surface. The apical cell surface of the epithelial membranes either was irregular or possessed microvilli, but the cell surface in the groups of the polygonal cells was always irregular. This varying ultrastructure of the cell surface of the cancer cells might imply a difference in the properties of these cells. However, no correlation of the appearance of the cell membrane with some consistent feature of the cytoplasm in the cancer cell was observed in the present investigation.

Several irregular projections from the surface of a cell are probably a sign that the cell membrane exhibits lively movements. Since the basal surfaces of normal epithelial cells are rather regular, most of the movements of this part of the cell membrane might be inhibited by the contact of the connective tissue cells. However, the low squamous type of the adenocarcinoma cells showed several long projections into the connective tissue. Since some cancer cells seem to lack the property of having the movements of their cell membrane inhibited by contact, the long projections of some adenocarcinoma cells might be signs of a reduced contact inhibition of these cells.

Cancer cells of different origin are known by both light and electron microscopy to show a higher variance in the number of intracellular structures than do the normal cells (14).
present investigation demonstrated that this is also valid in the cells of the uterine adenocarcinoma. The change mostly comprised a decrease, but sometimes the number of a cellular component was increased. This was the case, for example, with RNP particles and some of the cytoplasmic inclusions.

The higher amount of free RNP particles in the cytoplasm of some cells caused these cells to appear more dense than the other cells in the electron micrographs. These dense cells probably correspond to the A cells, introduced by Caspersson and Santesson (4). The density of these cells, however, seems to be caused not only by the RNP particles but also by some dense homogeneous material of the ground substance in the cell. A similar material was also present basally in those epithelial cells that were lacking the basement membrane. The significance of this material is not yet known.

Some cellular inclusions, such as lipide globules, vesicles, and granules, were more frequently observed in some cancer cells compared with the normal cells. The ultrastructures of the lipide globules and the small vesicles were similar to these inclusions in normal cells, but the large membrane-containing vesicles and the granules have not been observed in the normal human uterine epithelium. Probably, these structures are signs of degeneration in the cancer cells. It might also be that the granules are ingested bacteria.

Some mitochondria of the cancer cells were large and irregular. Similar mitochondria were also observed during the secretory phase of the menstrual cycle (6, 12, 17, 19). However, whereas the mitochondrial cristae of cancer cells were scanty and irregularly distributed, the mitochondrial cristae of the normal gland cells were parallel and tightly packed. Since the cancer cells containing the large mitochondria had the appearance of anaplasia, the arrangement of the cristae in these mitochondria might be a sign of dedifferentiation.

The results of the present investigation demonstrated that the ultrastructure of cells in the adenocarcinoma of the uterus varies. It was not possible to observe any cellular component or virus-like particle that might be specific for this type of cancer cell.

REFERENCES
FIG. 1.—Apical part of adenocarcinoma cells. The cell to the left has a dense cytoplasm. This cell is probably an A cell. The mitochondria of both the cells are rather large, and those of the A cell show changes of a degenerative type. Some granules are observed among the mitochondria of the cell to the right. Portions of nuclei are noticed in the lower part of the figure. Mag. ×21,000.

FIG. 2.—Apical part of adenocarcinoma cells. The cell surface possesses microvilli. Granules and small vesicles occur frequently in the cytoplasm. Portions of nuclei are noticed in the lower right- and left-hand parts of the picture. Mag. ×25,000.
Fig. 3.—Apical part of adenocarcinoma cells. The cell surface has an irregular course. Some large mitochondria with disordered inner lamellae are noticed. Some RNP-coated membranes are observed. Mag. X≥1,000.
Fig. 4.—Squamous type of adenocarcinoma cell with long processes into the connective tissue. Mag. ×7,000.

Fig. 5.—Apical part of adenocarcinoma cells. Several RNP-coated membranes are located at the nuclear membrane in close vicinity to a nucleolus. Mag. ×16,000.
FIG. 6.—Part of adenocarcinoma cells growing in a globelike cell group. The irregular cell membrane is noticed. The row of small vesicles from the surface into the cytoplasm might indicate pinocytosis. In the middle of the picture a part of a cell with a rather electron-dense cytoplasm is observed. This cell probably is an A cell. Lipide globules (L) also are noticed. Mag. X42,000.

FIG. 7.—Part of adenocarcinoma cell growing in a globelike cell group. Mitochondria, lipide globules (L), small vesicles, and lamellated bodies (arrows) are noticed. Mag. X42,000.
Fig. 8.—Basal part of a row of adenocarcinoma cells which are lacking the basement membrane. A zone of cytoplasm adjacent to the cell membrane has a dense ground substance, with few cell constituents. Mag. X26,000.

Fig. 9.—Part of adenocarcinoma cells growing in a globelike cell group. Among the different cell constituents, a vesicle containing a dense substance is noticed. The bounding membrane of the vesicle has ruptured. Mag. X19,000.
FIG. 10.—Part of adenocarcinoma cell growing in a globelike cell group. Mitochondria, lipide globules, small vesicles, large membrane-containing vesicles, and lamellated bodies are noticed. Mag. X47,000.
Fig. 11.—Part of adenocarcinoma cell growing in a globe-like cell group. Several large membrane-containing vesicles are noticed. Mag. X56,000.
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