Epithelial Polarity, Villin Expression, and Enterocytic Differentiation of Cultured Human Colon Carcinoma Cells: A Survey of Twenty Cell Lines

Isabelle Chantret, Alain Barbat, Elisabeth Dussaux, Michael G. Brattain, and Alain Zweibaum

ABSTRACT

Twenty human colon carcinoma cell lines were studied for their ability to develop some of the characteristics of the normal intestinal epithelium, e.g., epithelial polarity, presence of the actin-binding protein villin, or the occurrence of an enterocytic differentiation either when cultured under standard conditions, as for Caco-2 cells, or when grown in a glucose-free medium, as for HT-29 cells. Except for the regular presence of villin, which can be considered a marker of the colonic origin of the cells, the cell lines of this study could be classified into four types with regard to their differentiation characteristics. In type 1 (only one cell line, i.e., Caco-2) the cells undergo spontaneously an enterocytic differentiation characterized by a polarization of the cell layer with the formation of a brush border and the presence of an apical brush border membrane of which is endowed with hydrolases such as sucrase-isomaltase, lactase, aminopeptidase N, dipeptidylpeptidase IV and alkaline phosphatase. In type 2 (three cell lines: HT-29, HCT-EB, and HCT-GEO) the cells are undifferentiated when grown in the presence of glucose but undergo an enterocytic differentiation when grown in the absence of glucose. In type 3 (eight cell lines: HCT-GLY, HCT-FET, HCT-FRI, HCT-CBS, HCT-ALA, Co-115, HRT-18, and SW-1116) the cells are organized into a polarized monolayer with the formation of domes but without any enterocytic differentiation characteristics, whatever the culture conditions. In type 4 (eight cell lines: HCT-116a, HCT-R, HCT-RCA, HCT-Moser, HCT-8R, SW-480, LS-174T, and Vaco-9P) the cells are organized into a multilayer without any feature of epithelial polarity or enterocytic differentiation, whatever the culture conditions.

INTRODUCTION

Cultured human colon carcinoma cell lines provide a useful tool to understand how the neoplastic process interferes with the regulation of cellular differentiation. Only a limited number of colon cell lines have been characterized thus far with regard to differentiation features associated with the absorptive cells of the colon epithelium such as its ultrastructural morphology, its structural and functional polarity, or the expression of specific proteins. Cell polarity, as assessed by the ability of the cells to form domes when grown on an impermeable support (1), the presence of tight junctions, or vectorial transport properties, has been reported in six cell lines only, namely T84 (2, 3); Caco-2 (4, 5); HCA-7 (6); clones of HT-29 cells such as HT-29-19A (7, 8), HT-29-19C (9), and HT-29-19BC (5); HRT-18; and Co-115 (10). The occurrence of an enterocytic differentiation with the concomitant presence of an apical brush border and of brush border-associated hydrolases specific for the small intestine (11) and the fetal colon (12) has been reported in two cell lines only: Caco-2, in which it occurs spontaneously under standard culture conditions (13); and HT-29 cells which are differentiated only when adapted to grow in a glucose-free medium (14-16). The presence of villin, a Ca<sup>2+</sup>-regulated actin-binding protein known to be specifically associated with the cytoskeleton of the brush border microvilli (17), has been reported only in Caco-2 (18) and HT-29 cells (18-20). Surprisingly, villin was expressed in the latter cells even when undifferentiated, although at a lower level and with a different cellular localization (18-20). That other colon cell lines should also express some of these differentiation features is suggested by the observations that (a) villin is present in a number of colon tumors (18) and (b) an enterocytic differentiation is associated with some colon tumors (21). The purpose of the present work was to screen 20 established human colon carcinoma cell lines, with Caco-2 and HT-29 being used as controls, for the expression of cell polarity, the presence of villin, and their ability to develop an enterocytic differentiation, either when grown under standard culture conditions, such as Caco-2 cells, or when adapted to grow in a glucose-free medium, like HT-29 cells (14-16).

MATERIALS AND METHODS

Cell Lines and Culture Conditions. The 20 cell lines used were established lines developed from human colorectal adenocarcinoma. The cell lines HT-29 (22), SW-480 (23), SW-1116 (23), LS 174 T (24), and Caco-2 (25) were obtained from Dr. J. F. Fogh (Sloan Kettering Memorial Cancer Center, Rye, NY); HRT-18 (26) and HCT-8R (27) from Dr. W. A. F. Tompkins (University of Illinois, Urbana, IL); Co-115 (28) from Dr. J. K. V. Willson (William S. Middleton Memorial Veterans Hospital, Madison, WI). The cell lines HCT-ALA, HCT-CBS, HCT-EB, HCT-FET, HCT-FRI, HCT-CBS, HCT-GLY, HCT-Moser, HCT-R, HCT-RCA, and HCT-116a were established as reported (30). The cells were cultured in Dulbecco’s modified Eagle’s minimum essential medium (Eurobio, Paris, France) supplemented with 10% inactivated fetal bovine serum and 2.5 mM L-glutamine as reported previously (30). The culture medium was changed daily regardless of the culture condition investigated.

Enzyme Assays. Enzyme activities were performed on the cell homogenates (H) and on membrane fractions prepared according to the same protocol as used for the preparation of brush border-enriched fractions (P<sub>2</sub>) (31). Sucrase (EC 3.2.1.48) activity was measured according to the method of Messer and Dahlqvist (32), dipeptidylpeptidase IV (EC 3.4.14.5) according to that of Nagatsu et al. (33) using 1.5 mM glycyl-L-proline-4-nitroanilide as substrate, aminopeptidase N (EC 3.4.11.2) according to the method of Maroux et al. (34) using L-alanine-p-nitroanilide as substrate, alkaline phosphatase (EC 3.1.3.1) according to the method of Garen and Levinthal (35) with p-nitrophenylphosphate as substrate, and lactate dehydrogenase (EC 5.3.1.23) according to the method of Messer and Dahlqvist (32) with lactate as substrate, in the presence

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2 To whom requests for reprints should be addressed.
of 0.2 mM p-chloromercuribenzoate, an inhibitor of acid β-galactosidase (36). Results are expressed as milliunits/mg protein. One unit is defined as the activity that hydrolyzes 1 μmol of substrate per min at 37°C. Proteins were assayed by the method of Lowry et al. (37).

Antibodies. Mouse monoclonal antibody HBB 3/775/42 specific for dipeptidylpeptidase IV from human small intestine (38) was obtained from Dr. H. P. Hauri (Biocenter of the University of Basel, Basel, Switzerland). Polyclonal rabbit antibody against sucrase-isomaltase purified from Caco-2 cells was produced in rabbits (39). Rabbit polyclonal antibodies against porcine villin (18) were a gift from Dr. Daniel Louvard (Institut Pasteur, Paris, France). Anti-rabbit sheep antiglobulins labeled with horseradish peroxidase or fluorescein isothiocyanate were obtained from Institut Pasteur (Marnes-la-Coquette, France). Anti-mouse swine antiglobulins labeled with fluorescein isothiocyanate were obtained from Nordic Immunological Laboratories (Tilburg, The Netherlands).

Indirect Immunofluorescence. Indirect immunofluorescence assays were performed as reported previously (13, 15) on cells grown in plastic flasks.

Transmission Electron Microscopy. Transmission electron microscopy was performed as reported previously (13, 15) on cells grown in Petri dishes.

Immunoblotting of Villin. Cellular extracts for immunoblotting analysis of villin were prepared as follows. Cells grown on Petri dishes were rinsed three times with phosphate-buffered saline. To each dish were added 400 μl of 20 mM Tris buffer, pH 8.8 containing 2 mM CaCl2, 2% Triton X-100, and a cocktail of protease inhibitors (phenylmethylsulfonyl fluoride (1 mM), antipain (1 μg/ml), pepstatin A (1 μg/ml), and benzamidine (15 μg/ml)). After 5 min at room temperature, the mixture was centrifuged (2 min at 1,000 × g) and yielded one pellet (P1) and a supernatant (S1). S1 was centrifuged 2 min at 10,000 × g and yielded the second supernatant S2, which was stored at −70°C. Proteins of S2 (100 or 200 μg) were separated on 7.5% sodium dodecyl sulfate-polyacrylamide gel electrophoresis in the buffer system of Laemmli (36). Results are expressed as milliunits/mg protein. One unit is defined as the activity that hydrolyzes 1 μmol of substrate per min at 37°C. Proteins were assayed by the method of Lowry et al. (37).

RESULTS

Epithelial Polarity. The different cell lines could be classified into three groups on the basis of their ability to form a polarized epithelium, as judged by phase contrast and transmission electron microscopy (Table 1). Group 1 (10 cell lines) was characterized by the formation of domes which occurred after the cells had reached confluency. The size and number of domes varied from one cell line to another. Their morphology at phase contrast microscopy (Fig. 1) was the same as already reported for other dome-forming cell lines. At transmission electron microscopy all dome-forming cell lines appeared as polarized monolayers with the presence of apical tight junctions (Fig. 2). With the exception of Caco-2 cells (13) none of these cell lines displayed an apical brush border; only irregular microvilli were present on the apical surface of the cell layer (Fig. 2, inset). Group 2 (HT-29, HCT-GEO, and HCT-EB) was characterized by the presence, at phase contrast microscopy, of intercellular cysts (Fig. 3), the total surface of which covered 50% of the cell layer of HCT-GEO and HCT-EB at late stationary phase. At transmission electron microscopy these cysts were of two types, concomitantly present in each cell line; some were lined with a regular and well organized brush border (Fig. 4a) whereas others were devoid of it (Fig. 4b). In both types of cysts the cells were polarized with the presence of apical tight junctions towards the lumen of the cysts (Fig. 4). Except for the presence of these cysts the general organization of the cell layer was that of a nonpolarized multilayer with no brush border being present at its apical surface, i.e., towards the culture medium (Fig. 4b).

In Group 3 (8 cell lines) neither domes nor cysts could be observed at phase contrast microscopy. At transmission electron microscopy the cells which were examined formed a multilayer with no apical tight junctions or brush border as already shown for some of the cell lines of this group such as SW-480 or HCT-8R cells (10).

Expression of Villin. Villin, as detected in cellular extracts by “Western blot” analysis, was present in all the tested cell lines grown under standard culture conditions. However, apparent quantitative differences of expression from one cell line to another were observed (Fig. 5). The degree of expression of villin was independent of both the polarization and the differentiation of the cells (Table 1).

Enterocytic Differentiation. Previous experience showed that the differentiation of Caco-2 and HT-29 cells was complete and optimum only late after confluency (13-16). Consequently, all cell cultures in the present study were evaluated 30 days after seeding. With the exception of Caco-2 cells none of the 19 other cell lines exhibited any sign of enterocytic differentiation when grown under standard culture conditions, i.e., in the presence of glucose. This was demonstrated by: (a) the absence of immunofluorescent staining of the cell layers with antibodies directed against brush border-associated hydrolases (see Fig. 8a); (b) the activities of brush border-associated hydrolases which were tested in both the cell homogenates (H) and a membrane-enriched fraction (P2) and were found to be either absent, as in the case of sucrase and lactase, or very low, as in the case of dipeptidylpeptidase IV, aminopeptidase N, and alkaline phosphatase (Table 1); and (c) the low enrichment factor of enzyme activities (P2/H) which was always much lower than found in Caco-2 cells (Table 1) and was consistent with the absence of an apical brush border as disclosed by transmission electron microscopy.

In order to find out whether some of these cell lines would express an enterocytic differentiation when grown in glucose-free medium, 15 cell lines, including HT-29 cells used as a control, were switched to inosine-supplemented glucose-free medium. These cell lines were passaged every 10 days and tested for their differentiation characteristics on day 30 of passage 5, a passage number which has been found to be optimum for the highest degree of differentiation of HT-29 cells in such glucose-free culture conditions (16). Only two cell lines (HCT-GEO and HCT-EB), in addition to the previously described HT-29 cells (14-16), exhibited signs of enterocytic differentiation when cultured in the absence of glucose. Under such culture conditions both cell lines formed a polarized monolayer with the presence of an apical brush border (Figs. 6 and 7). The degree and type of enzymatic differentiation of both cell lines were, however, different from those observed in HT-29 cells (Table 2). HCT-EB cells exhibited an enzymatic differentiation restricted to the expression of dipeptidylpeptidase IV (Fig. 8) and alkaline phosphatase (Table 2); no brush border-associated hydrolases could be detected in differentiated HCT-GEO cells as disclosed by the absence or immunofluorescent reactivity of the cell layer with anti-hydrolase antibodies (not shown) and the absence of increase of enzyme activities (Table 2).

DISCUSSION

The results reported here show that some of the differentiation features normally associated with the structural or functional organization of the absorptive cells of the colonic epithelium are either totally, partially, or not at all preserved in...
Table 1  Polarization and differentiation characterization of 20 cultured human colon carcinoma cell lines grown under standard culture medium conditions (25 mm glucose)

<table>
<thead>
<tr>
<th>Cell lines</th>
<th>Polarization</th>
<th>Electron microscopy</th>
<th>Specific enzyme activities*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TJ* S</td>
<td>DPP-IV</td>
</tr>
<tr>
<td>Caco-2</td>
<td>Domes</td>
<td>+  +</td>
<td>14</td>
</tr>
<tr>
<td>HT-29</td>
<td>Cysts</td>
<td>+  +</td>
<td>0</td>
</tr>
<tr>
<td>HCT-GLY</td>
<td>Domes</td>
<td>+  -</td>
<td>0</td>
</tr>
<tr>
<td>HCT-FET</td>
<td>Domes</td>
<td>+  -</td>
<td>0</td>
</tr>
<tr>
<td>HCT-FRI</td>
<td>Domes</td>
<td>+  -</td>
<td>0</td>
</tr>
<tr>
<td>HCT-CBS</td>
<td>Domes</td>
<td>+  -</td>
<td>0</td>
</tr>
<tr>
<td>HCT-ALA</td>
<td>Domes</td>
<td>+  -</td>
<td>0</td>
</tr>
<tr>
<td>HCT-GEO</td>
<td>Cysts</td>
<td>+  +</td>
<td>0</td>
</tr>
<tr>
<td>HCT-EB</td>
<td>Cysts</td>
<td>+  +</td>
<td>0</td>
</tr>
<tr>
<td>HCT-116s</td>
<td>ND</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HCT-R</td>
<td>ND</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>HCT-RCA</td>
<td>ND</td>
<td>0</td>
<td>0</td>
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<tr>
<td>HCT-Moser</td>
<td>ND</td>
<td>0</td>
<td>0</td>
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<tr>
<td>HCT-8R</td>
<td></td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Co-115</td>
<td>Domes</td>
<td>+  -</td>
<td>0</td>
</tr>
<tr>
<td>HRT-18</td>
<td>Domes</td>
<td>+  -</td>
<td>0</td>
</tr>
<tr>
<td>SW-480</td>
<td></td>
<td>-  -</td>
<td>0</td>
</tr>
<tr>
<td>LS-174T</td>
<td></td>
<td>-  -</td>
<td>0</td>
</tr>
<tr>
<td>SW-1116</td>
<td>Domes</td>
<td>+  -</td>
<td>0</td>
</tr>
<tr>
<td>Vaco-9P</td>
<td>Cysts</td>
<td>+  +</td>
<td>0</td>
</tr>
</tbody>
</table>

* Enzyme activities were measured after 30 days in culture. Results are the mean of 5 different passages. SD (not shown) are less than 5%.
^ Results correspond to the intensity of the bands of immunoblotting (see Fig. 5), with lanes 1, 2 corresponding to ++++, lanes 3, 4 to ++, and lanes 5, 6 to +.
TJ, tight junctions; BB, brush border; L, lactase; S, sucrase; DPP-IV, dipeptidylpeptidase IV; APN, aminopeptidase N; AP, alkaline phosphatase; ND, not done.
* Enzyme activity in the cell homogenates (H).
Enrichment factor (ratio of activity P2/H).
MARKERS OF COLONIC CELL LINES

Fig. 1. Phase contrast micrograph showing the presence of domes in post-confluent cultures of (a) Co-1 IS (focused on the monolayer) and (b) HCT-GLY cells (focused on the top of the dome). x 70.

Fig. 2. Transmission electron microscopy of postconfluent (day 30) SW-1116 cells, x 3,850. Sections are perpendicular to the bottom of the flask. Note the organization of the cells into a polarized monolayer with the presence of tight junctions (arrow and inset, x 18,200). Note the presence of irregular microvilli.

Fig. 3. Phase contrast micrograph of the cell layer of HCT-EB cells (day 30) grown in a standard culture medium (i.e., in the presence of glucose). Note the presence of very numerous intercellular cysts, x 100.

Villin appears to be the most regularly preserved colonic marker as it is present, although at different levels, in all the 20 cell lines of this study. Its expression is independent of both the polarization and the differentiation of the cells. This observation is in good agreement with previous results which showed that villin is regularly present in colon cancers, whatever their degree of differentiation (18). That villin is also regularly expressed in cultured cell lines derived from colon cancers further confirms the interest of this protein as a marker of the colonic origin of colon cancer cells (18–20).

With regard to the morphological and functional differentiation characteristics normally associated with the absorptive cells of the adult or fetal colon the cell lines of this study can be classified into four main types.

Type 1: Cell Lines Which Express Spontaneously the Differentiation Characteristics of Mature Enteroctyes. Only one cell line has been found thus far to belong to this type, namely Caco-2. The differentiation of these cells is characterized by the concomitant association of three criteria: (a) the organization of the cells into a polarized monolayer; (b) the presence of an apical brush border; and (c) the presence of brush border-associated hydrolases such as sucrase-isomaltase, lactase, aminopeptidase N, dipeptidylpeptidase IV, and alkaline phosphatase (13, 38). As reported previously this type of differentiation is close to that found in the fetal colon (12, 21, 38, 43, 44). Since the same type of differentiation has been observed in some colon cancers (21) it is most likely that other colon carcinoma cell lines, which have not been investigated yet, should express spontaneously the same type of differentiation.

Type 2: Cell Lines the Differentiation of Which Can Be Modulated. Three cell lines belong to this type, namely, HT-29, HCT-EB, and HCT-GEO. These cell lines are undifferentiated when grown under standard culture conditions, i.e., in the presence of glucose. Their differentiation occurs only when...
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Fig. 4. Transmission electron microscopy of (a) HCT-EB (x 3,000) and (b) HCT-GEO (x 1,500) cells showing the two morphological types of intercellular cysts with the presence (a) or absence (b) of an ultraluminal brush border. Sections are perpendicular to the bottom of the flask. Cells were examined after 30 days in culture in the presence of glucose.

Fig. 5. Immunological detection of villin in cellular extracts analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis transferred onto nitrocellulose sheets. Cells were tested at day 30 of culture under standard conditions. Lane 1, Caco-2; Lane 2, Vaco-9P; Lane 3, HCT-116; Lane 4, SW-480; Lane 5, LS-174T; Lane 6, SW-1116. The same quantity of protein was loaded in each slot. Similar results were obtained with cell extracts from the other 14 cell lines (see Table 1). kD, molecular weight in thousands.

they are grown in the absence of glucose. Under such culture conditions they display a morphological enterocytic differentiation characterized by the organization of the cells into a polarized monolayer with the presence of an apical brush border. They differ, however, as to their degree of enzymatic differentiation: HT-29 cells express the same hydrolases as Caco-2 cells, except for lactase; HCT-EB express only dipeptidylpeptidase IV and alkaline phosphatase; whereas HCT-GEO differentiated cells express no enzymes at all. The particularities of this type of cell raise at least two questions. (a) Why would these three cell lines only, but not others, undergo a modulatable differentiation? (b) Why would the absence of glucose allow the differentiation of these cells? Thus far these questions remain unanswered. Concerning the first question and with regard to the analogy which can be established with fetal differentiation it is of interest to note that HT-29, HCT-EB, and HCT-GEO cells display, when undifferentiated, intercellular cysts which closely resemble the “secondary lumens” observed in the early stages of intestinal development (45, 46). The reason why the absence of glucose in the culture medium permits the differentiation of these three cell lines remains a challenging and unanswered question. There are, however, some lines of evidence that the alterations of glucose metabolism associated with the neoplastic process may interfere with the overall regulation of the differentiation of the cells (for review see Ref. 47): in Caco-2 cells an inhibition of the expression of sucrase-isomaltase has been shown to be concomitant with an increase of glucose utilization in cells treated with forskolin (48) and monensin (49); whereas in HT-29 cells grown in the presence of glucose the absence of expression of sucrase-isomaltase has been shown to be a consequence of an impairment of the post-translational processing of the enzyme (39).

Fig. 6. Transmission electron microscopy of postconfluent (day 30) HCT-GEO cells grown for 5 passages in inosine-supplemented glucose-free medium. Section is perpendicular to the bottom of the flask. x 3,300. Note the organization of the cells into a polarized monolayer with an apical brush border. Compare with the same cells grown in the presence of glucose (Fig. 46).
MARKERS OF COLONIC CELL LINES

Fig. 7. Transmission electron microscopy of postconfluent (day 30) HCT-EB cells grown in the presence of glucose (a) or after 5 passages in inosine-supplemented glucose-free medium (b, c). Sections are perpendicular to the bottom of the flask. In a, the cells are undifferentiated and form a nonpolarized multilayer. × 1,000. In b, the cells are organized into a polarized monolayer with the presence of tight junctions and a well developed apical brush border. × 3,000. c, higher magnification of a detail of b, (× 20,000) showing a tight junction and regular brush border microvilli.

Table 2 Effect of glucose deprivation on the enzymatic differentiation of HT-29, HCT GEO, and HCT EB cells

<table>
<thead>
<tr>
<th>Specific activity (milliunits/mg protein)</th>
<th>Cells grown in the presence of 25 mM glucose*</th>
<th>Cells grown for 5 passages in inosine supplemented glucose-free medium</th>
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<tr>
<td></td>
<td>S</td>
<td>L</td>
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<tr>
<td>HT-29</td>
<td>H</td>
<td>ND</td>
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<tr>
<td></td>
<td>P1</td>
<td>ND</td>
</tr>
<tr>
<td>HCT GEO</td>
<td>H</td>
<td>ND</td>
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<td></td>
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<tr>
<td>HCT EB</td>
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<td>ND</td>
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<td></td>
<td>P1</td>
<td>ND</td>
</tr>
</tbody>
</table>

* Cells were tested after 30 days in culture.

Fig. 8. Immunofluorescence staining with monoclonal antibody against dipeptidylpeptidase IV of postconfluent (day 30) HCT-EB cells grown in the presence of glucose (left) or after 5 passages in inosine-supplemented glucose-free medium (right). Note the absence of binding of the antibodies to the cell surface of glucose-fed cells (left) and the presence of an apical staining in glucose-deprived cells (right). × 380.

villi and without any significant expression of brush border-associated hydrolases. Whatever the culture conditions this type appears to be more frequent than should be expected from the limited number of dome-forming colonic cell lines reported in the literature (4–8, 10), as was found in 8 of the 20 cell lines of this study.

Type 4: Undifferentiated Unpolarized Cell Lines. These cell lines grow as multilayers of unpolarized cells and do not display any differentiation features such as brush border microvilli or brush border-associated hydrolases. Interestingly these cell lines with no apparent personality represent less than one-half of the cell lines of this study.

These four types of cells already appear, because of the differences in their organization, differentiation, and sensitivity to differentiation-permissive conditions, as potential tools for studying, at the cellular and molecular levels, the mechanisms which underlie the regulation of the expression of a number of cellular constituents and functions associated with the intestinal epithelium as well as the levels where the neoplastic process interferes with these mechanisms. Whether these different cell types may have any prognostic significance with regard to the

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original tumor is still an unanswered question and remains an open field of investigation.

REFERENCES


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