

Small mucus-granule-containing ciliated cells in the human gastric mucosa: a transitional form to metaplastic ciliated cells

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Summary. Ciliated cells were found in the gastric mucosa in close association with intestinal metaplasia, mainly in the pyloric mucosa, of Japanese patients. The occurrence of ciliated cells is believed to be an acquired phenomenon and is considered to be a type of metaplasia; the term “ciliated metaplasia” is used to describe this phenomenon. Ciliated cells are found in the basal part of the glands among normal-looking mucous cells, mucous neck cells and neuroendocrine cells, but never on the surface or in foveolar epithelium. In ciliated cell-containing glands, mitoses were noted in the neck region and the ultrastructural features of these cells were identical to those of undifferentiated neck cells. However, cell metaplasia from undifferentiated cells to metaplastic ciliated cells has never been demonstrated previously. The small mucus-granule-containing ciliated cells found in our present study may arise subsequent to division of undifferentiated neck cells into mucous cells with some daughter cells then exhibiting differentiation characteristics specific to ciliated cells. Thus they contain a mixture of both small mucus granules and numerous basal bodies and cilia, at the same time as a transitional form.

Key words: Mucus-granule-containing ciliated cell – Ciliated metaplasia – Transitional form – Gastric mucosa – Ultrastructure

Introduction

Recently, ciliated cells have been found in the human gastric mucosa, frequently in the pyloric glands, rarely in the cardiac glands, but always in association with intestinal metaplasia (Rubio and Kato 1986; Kawakita 1987; Torikata et al. 1986, 1989b, 1989c). The normal human gastric epithelium of fetuses and adults contains no ciliated cells (Rubin et al. 1968) and this phenomenon

is therefore considered to be acquired. It represents a metaplastic change in the gastric epithelium and the new term “ciliated metaplasia” has therefore been coined (Torikata et al. 1986; Rubio and Kato 1986). However, the pathological significance of ciliated gastric cells remains unclear, and cellular metamorphosis to ciliated cells has not been demonstrated previously.

In this paper, the authors present electron micrographs of small mucus-granule-containing ciliated cells in the human pyloric mucosa which are morphologically similar to the pre-ciliated cells found in the respiratory epithelium (Keenan 1987). We discuss a possible pathway from the undifferentiated neck cell to the metaplastic ciliated cell.

Materials and methods

Stomachs used in this study were obtained from material surgically resected because of gastric malignancy. Pyloric mucosa fixed with 10% formalin solution was cut and processed for routine histological examination. Sections of paraffin-embedded tissues were cut (3 µm) and stained with haematoxylin and eosin (H & E), periodic acid-Schiff (PAS) stain following diastase digestion, alcian blue, mucicarmine, Grimelius and Fontana-Masson stains. For electron microscopy, the fresh pyloric mucosa of aged patients resected for gastric carcinoma were fixed with 1% tannic acid containing 1% glutaraldehyde, post-fixed with 1% osmium tetroxide, and embedded in Spurr's resin (Spurr 1969). Ultrathin sections were cut, double-stained with uranyl acetate and lead nitrate and examined using a JEOL 100C electron microscope at 100 kV.

Results

Ciliated cells in the human pyloric mucosa were observed in the basal part of the glands in association with intestinal metaplasia. Ciliated cells were fairly large, cuboidal, slightly eosinophilic, and exhibited no mitotic activity. Cilia were noted on the apical surface, often in the concave channels. Most ciliated cells were negative with respect to various mucus stains, and they never stained positive in Grimelius or Fontana-Masson stains.

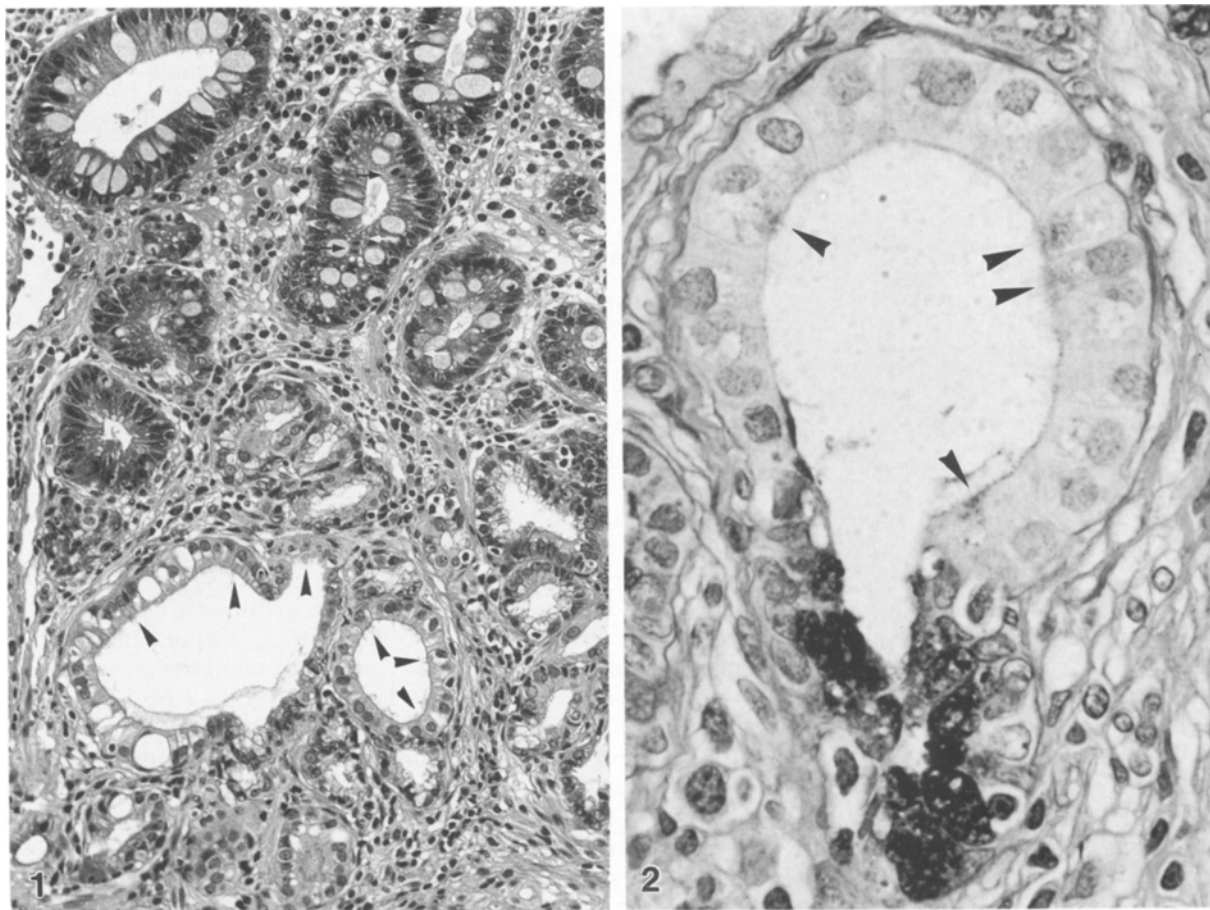


Fig. 1. Ciliated cell-containing pyloric glands of the human stomach. Ciliated cells are noted in the basal part of the glands (*arrowheads*) and, in the upper part, metaplastic goblet cells are noted. Mitotic cells (*arrows*) are seen in the neck region. H & E, $\times 200$

Fig. 2. PAS-positive, granule-containing ciliated cells in a human pyloric gland. Numerous ciliated cells are lined up, forming a gland. On the apical surface, numerous cilia are noted. PAS staining reveals four ciliated cells (*arrowheads*) containing PAS-positive small granules in the supranuclear region. PAS, $\times 800$

However, a very few ciliated cells located near the neck of the glands stained positive with PAS, but these ciliated cells contained no large mucin-negative vacuoles in the cytoplasm. Ciliated cell-containing glands not infrequently exhibited cystic dilatation of their basal portions and were lined up in considerable numbers. Some contained large mucus-negative vacuoles in the cytoplasm. Mitoses were noted in the neck, but not in the basal part of the gland (Figs. 1, 2).

Electron microscopy revealed ciliated cells occurring singly or in small clusters among the pyloric mucous cells, the mucous neck cells and neuroendocrine cells in the basal part of the glands. Ciliated cells contained abundant cytofilaments and in the supranuclear region, lipid droplets and sometimes lamellar structures and large vacuoles. Cilia were noted on the apical surface of the cell and sometimes in the concave channels and were mixed with fairly long microvilli; however, there

were fewer cilia per cell than in respiratory ciliated cells. These ciliated cells contained neither mucus granules nor neuroendocrine granules (Fig. 3).

The undifferentiated cells in the neck of the gland contained a nucleus and prominent nucleoli, an extensive cytoplasmic matrix containing numerous ribosomes, few mucus granules and a large proportion of agranular endoplasmic reticulum and mitochondria. Microvilli were noted on the apical surface. Mitoses were seen on electron microscopy (Fig. 4). The mucous neck cells were lined up in the neck region and contained fairly large mucus granules in the apical portion; however, with the exception of the mucus granules, ultrastructural morphology was almost the same as that of the undifferentiated neck cell.

Small mucus-granule-containing ciliated cells were noted in the lower part of the neck of the glands and were surrounded by undifferentiated neck cells, mucous neck cells and neuroendocrine cells, sometimes forming a small cluster (Fig. 5). These specific cells contained both small mucus granules, 100–150 nm in diameter, and numerous basal bodies, and these both frequently formed clusters in the apical portion (Fig. 6A). The mucus granules were smaller than in the mucous neck cells and pyloric mucous cells (Fig. 6B). With the exception of the mucus granules and basal bodies, ultrastructural findings were similar to those of undifferentiated neck cells.

Small mucus-granule-containing ciliated cells have

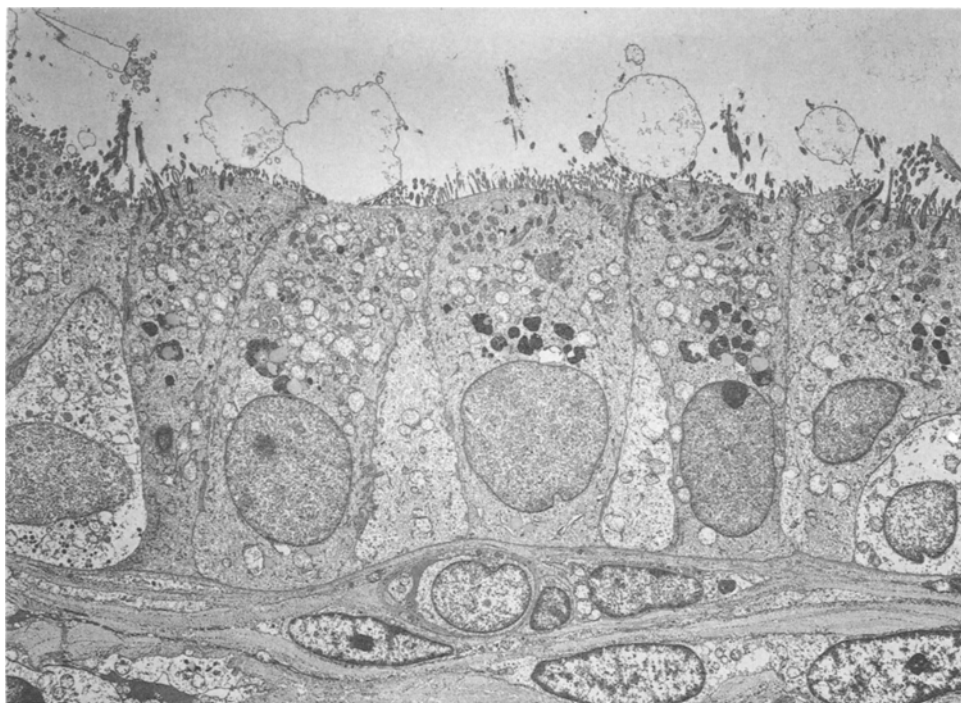


Fig. 3. Metaplastic ciliated cells in the human pyloric mucosa. Ciliated cells are seen on a basal lamina, and numerous cilia are noted on the cell surface mixed with microvilli. In the supranuclear region, prominent lipid droplets are seen, but no mucus granules are seen in the cytoplasm. $\times 2200$

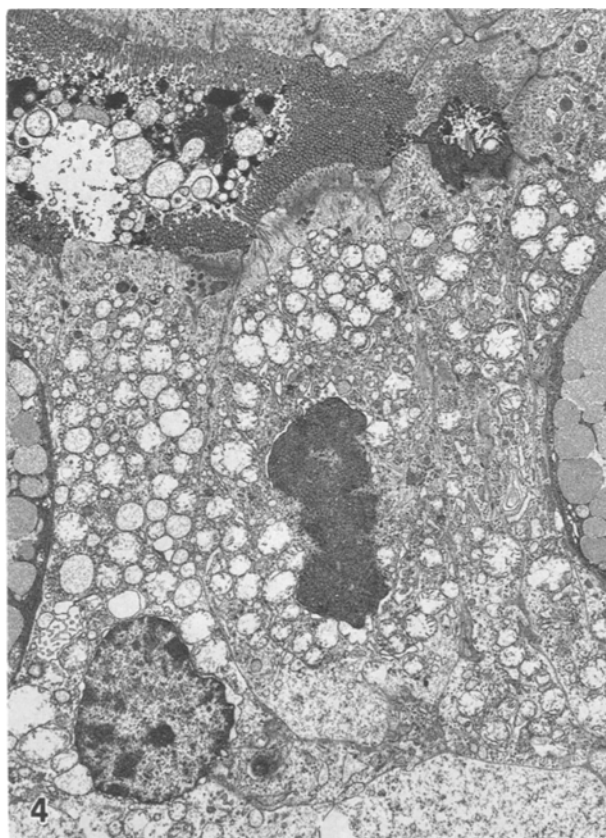


Fig. 4. Undifferentiated neck cells of a human pyloric gland. Three undifferentiated neck cells are seen between metaplastic goblet cells, and the centre one is undergoing mitosis. They contain numerous ribosomes, dilated mitochondria and endoplasmic reticulum, but no mucus granules in the cytoplasm. $\times 3600$



Fig. 5. A small mucus-granule-containing ciliated cell in a human pyloric gland. A single small mucus-granule-containing ciliated cell is seen among undifferentiated neck cells. In the apical region, a cluster consisting of numerous small mucus granules and numerous basal bodies can be seen (arrowhead), and on the cell surface, numerous microvilli lacking cilia are seen. $\times 3600$

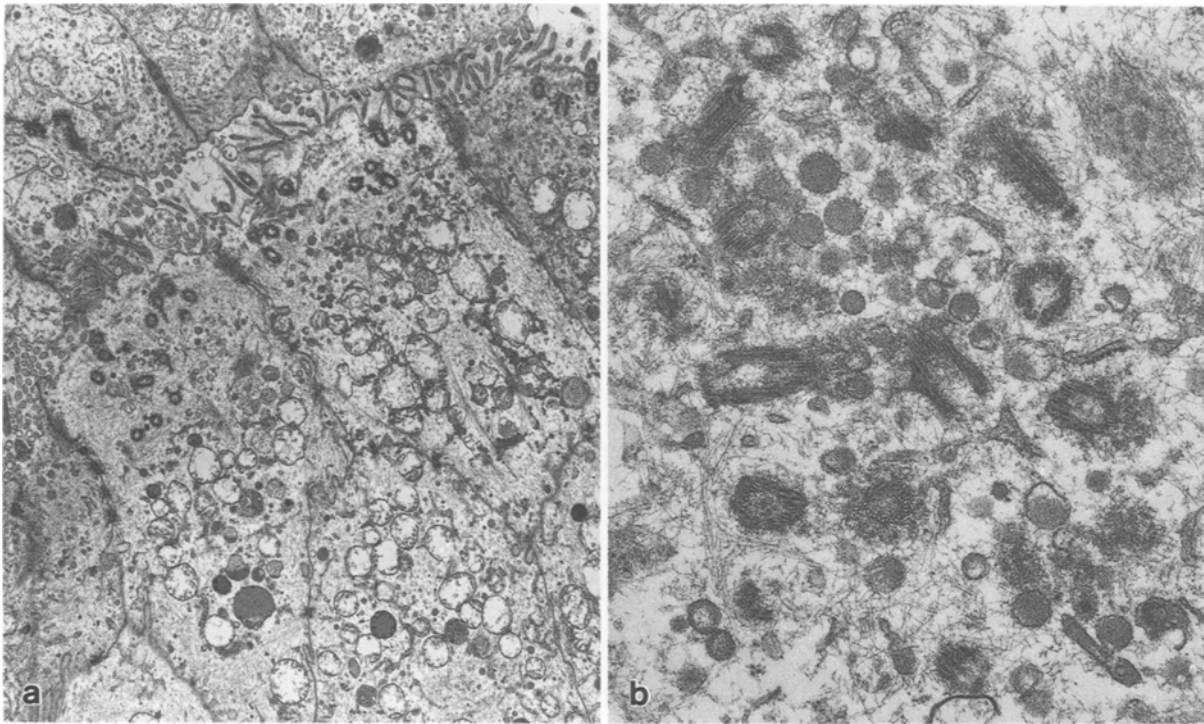


Fig. 6A, B. Apical portion of small, mucus-granule-containing ciliated cells. Numerous basal bodies, cilia and small mucus-granules are seen in the apical portion of two cells. In the right one, basal bodies have moved to the cell surface, and small mucus granules remain in the apical cytoplasm (A). The mucous granules contain electron-dense amorphous substance within a cellular membrane, and their diameter is about 100–150 nm (B). A $\times 7000$, B $\times 24000$

been found in the pyloric mucosa of two 73-year-old male patients with gastric carcinoma.

Discussion

Ultrastructural observations of ciliated cells in the human gastric mucosa have been reported in association with intestinal metaplasia, mainly in Japanese patients (Kodaira et al. 1974; Okuda and Ogata 1976; Kawamata et al. 1986; Kawakita 1987; Torikata et al. 1986, 1989b, 1989c). The occurrence of these ciliated cells is believed to be an acquired phenomenon, and a new term “ciliated metaplasia” has been coined to describe it (Torikata et al. 1986; Rubio and Kato 1986); however, no pathway to metaplastic ciliated cells has been demonstrated. Only the presence of ciliated cells and a close association with intestinal metaplasia in the stomach have been reported. With respect to intestinal metaplasia of gastric epithelium, various types of epithelial cells encountered in metaplastic foci are found to be identical to normal intestinal epithelial cells both morphologically and functionally and this is the basis for referring to this phenomenon as intestinal metaplasia. However, ciliated cells are not included among the constituents of so-called intestinal metaplasia of the stomach and the pathological significance of this phenomenon remains unclear.

This report is the first to demonstrate a transitional form between normal gastric epithelial cells and metaplastic ciliated cells ultrastructurally. Pre-ciliated cells have been demonstrated in respiratory epithelium during the repair process after injury (Keenan 1987). In normal bronchi, small mucus granule cells (SMGC) in the bronchial epithelium have mitotic activity and have been discussed as multipotential reserve cells (McDowell et al. 1982)). Ciliated-secretory cells have been demonstrated to be transitional forms (Jeffrey 1983). In the normal gastric mucosa, mitotic cells are always found in the neck of the glands and referred to as undifferentiated neck cells (Bloom and Fawcett 1975). In the metaplastic regions, mitoses are also noted in the neck, but never in the basal part of the gland, and the cells undergoing mitosis are identical to undifferentiated neck cells ultrastructurally. Metaplastic ciliated cells in the gastric mucosa have always been associated with so-called intestinal metaplasia, and have been found in the lower part, mostly in the basal part of the glands, and never on the surface or in foveolar epithelium (Kawakita 1987; Torikata et al. 1989b).

Metaplastic ciliated cells have been found in pyloric (Kodaira et al. 1974; Okuda and Ogata 1976; Rubio and Kato 1986; Kawakita 1987; Torikata et al. 1986, 1989b) and cardiac glands (Torikata et al. 1989c) in close proximity to mucous cells, but not in close proximity to the chief cells in gastric glands. In this study, small mucus-granule-containing ciliated cells were found in metaplastic mucosa, but no small mucus-granule-containing cells, like the SMGC in the bronchial epithelium, were found; in the gastric mucosa, only undifferentiated neck cells possess mitotic activity. Therefore, a direct metaplastic relationship between mucous neck cells and small mucus-granule-containing ciliated cells is uncer-

tain. However, the occurrence of small mucus granules in the neck cells might represent an initial stage of mucus production and be indicative of differentiation into PAS-positive mucous cells. In the process of differentiation into mucous cells, such small mucus-granule-containing cells may arise subsequent to the division of undifferentiated neck cells. The daughter cells which then exhibit differentiation characteristics specific to ciliated cells may display a mixture of small mucus-granules and numerous basal bodies. The small mucus granules in these metaplastic cells probably disappear soon after ciliogenesis starts. Metaplastic ciliated cells in human pyloric glands sometimes contain large mucus-negative vacuoles in the cytoplasm (Torikata et al. 1989a); however, small mucus-granule-containing ciliated cells never contain such vacuoles, suggesting that these cells might be newly formed by division of undifferentiated neck cells. It is still not clear what mechanical or chemical stimuli give rise to the genetic abnormalities which change undifferentiated neck cells into metaplastic, ciliated cells.

References

- Bloom W, Fawcett D (1975) Cell renewal and regeneration in the stomach. In: Bloom W, Fawcett D (eds) *A textbook of histology*. 10th ed. Saunders, Philadelphia, pp 655–657
- Jeffrey PK (1983) Morphologic features of airway surface epithelial cells and glands. *Am Rev Respir Dis* 128 [Suppl]:14–20
- Kawakita H (1987) Ciliated cells in human stomach. *Studies on resected cases* (in Japanese). *Keio Igaku* 54:87–102
- Kawamata S, Kubota Y, Sawataishi M, Takaya K (1986) The fine structure of atypical ciliated cells in the human gastric epithelium. *Virchows Arch [B]* 51:363–374
- Keenan KP (1987) Cell injury and repair of the tracheobronchial epithelium. In: McDowell EM (ed) *Lung carcinoma*. Churchill Livingstone, Edinburgh, pp 74–93
- Kodaira T, Watanabe Y, Arimori M (1974) Ciliated epithelium in gastric mucosa observed in chronic gastritis. An electron microscopy study (in Japanese). *Proceedings of the 33rd Annual Meeting of the Japan Cancer Association*. (Sendai), Japanese Cancer Association, p 184
- McDowell EM, Harris CC, Trump BF (1982) Histogenesis and morphogenesis of bronchial neoplasms. In: Shimosato Y, Melamed MR, Nettesheim P (eds) *Morphogenesis of lung cancer*, vol 1. CPC Press, Boca Raton, pp 1–36
- Okuda T, Ogata T (1976) An electron microscopic study of the ciliated cells in the human gastric mucosa. *Arch Histol Jpn* 39:149–156
- Rubin W, Ross LL, Sleisenger MH, Jeffries GH (1968) The normal human gastric epithelia. A fine structural study. *Lab Invest* 19:598–626
- Rubio CA, Kato Y (1986) Ciliated metaplasia in the gastric mucosa. *Studies on Japanese patients*. *Jpn J Cancer Res* 77:282–286
- Spurr AR (1969) A low-viscosity epoxy resin embedding medium for electron microscopy. *J Ultrastruct Mol Struct Res* 26:31–43
- Torikata C, Mukai M, Kawakita H, Kageyama K (1986) Ciliated cells in human metaplastic gastric mucosa. A proposal of a new term “ciliated metaplasia.” *J Electron Microsc 35*:[Suppl] 3549–3550
- Torikata C, Mukai M, Kawakita H (1989a) Ultrastructure of the mucus-negative vacuolated cells in the metaplastic pyloric gland of the human stomach. *Hum Pathol* 20:437–440
- Torikata C, Mukai M, Kawakita H (1989b) Ultrastructure of metaplastic ciliated cells in human stomach. *Virchows Arch [A]* 414:113–119
- Torikata C, Mukai M, Kawakita H (1989c) Ciliated cells in the cardiac gland of the human stomach. *Acta Pathol Jpn* 38:388–392