Do Stem Cells Participate in Cell Turnover in Duodenal Adenomas? A Preliminary Study on Paneth Cells

CARLOS A. RUBIO

Gastrointestinal and Liver Pathology Research Laboratory, Department of Pathology, Karolinska Institute and Hospital, 171 76 Stockholm, Sweden

Abstract. Background: In the normal duodenum, Paneth cells migrate from the stem cells downwards, towards the bottom of the crypts of Lieberkuhn. Materials and Methods: The spatial position of Paneth cells within the profile of histological sections was investigated with hematoxilin and eosin (H&E) in 6 duodenal adenomas; 2 of them were also immunostained with lysozyme, an enzyme present in Paneth cells. Results: In H&E stain sections, the numbers of mature Paneth cells/high power field varied from 2 to 7 (mean 4.5). In the two immunostained adenomas, the numbers of lysozyme-expressing cells/high power field were 15 and 42, respectively. The lysozyme-stained cells were present at all levels in the adenomas, including the luminal epithelial layer. Conclusion: In duodenal adenomas, not all Paneth cells detected by lysozyme immunostain are apparent in H&E-stained sections, suggesting that lysozyme immunostain also detects Paneth cells precursors. Since mature Paneth cells and their precursors are positioned beneath the stem cells, it is conceivable that the Paneth cells that had reached the luminal aspect of the adenomas, were preceded by stem cells. This possibility would imply that in duodenal adenomas, the stem cells would be subjected to the same laws that orchestrate the turnover of epithelial duodenal cells, including Paneth cells and their precursors.

In 1872 (1) Schwalbe described a particular type of granulated cell in the small intestine. Sixteen years later, Joseph Paneth (1857-1890), an Austrian physician, studied the morphology of these cells in detail (2). Sir Alexander Fleming unveiled the functional significance of Paneth cells by discovering lysozyme, one of the natural defense substances against infections (3).

Paneth cells are normally found at the bottom of the crypts of Lieberkuhn in the small intestine but they may also be present in the cecum and the proximal colon. As metaplastic cells, Paneth cells may be found in Barrett’s esophagus, in gastric intestinal metaplasia, in chronic inflammation in the transverse, distal colon and rectum, the gall bladder with cholelithiasis, the urinary bladder, the prostate, the epididymis and the uterine cervix (cfr 4).

Paneth cells derive from a progenitor epithelial cell, called a stem cell (5-8). The stem cells constantly replenish the epithelial make-up with three other specialized epithelial cells: absorptive enterocytes, goblet cells and enteroendocrine cells. The latter three cell types migrate from the stem cell, upward towards the lumen of the organ, whereas Paneth cells migrate from the stem cell downwards towards the base of the crypts, where they reside for about 20 days before being engulfed by phagocytes (9).

Paneth cells secrete lysozyme and α-defensins, termed cryptdin (5-7), key peptides that keep the small intestine free from pathogenic bacteria, both in newborns and adults. These peptides have hydrophobic and positively-charged domains that can interact with phospholipids in cell membranes. Due to the higher concentration of negatively-charged phospholipids in bacteria, defensins preferentially bind to and disrupt microbial membranes (5-7).

Neoplasias originating in Paneth cells are rare. In the gastrointestinal tract (GI), isolated cases of Paneth cell neoplasia were reported in the stomach, jejunum, ileum, Meckel’s diverticulum, rectum, gall bladder and at extraintestinal sites such as the urinary bladder, uterine cervix and prostate (cfr 4).

In a recent survey, the frequency of duodenal adenomas showing gastric metaplasia was assessed (10). It became apparent that Paneth cells could be found at various levels within the adenomatous structures. The question arises as to whether stem cells could likewise occur at various levels in duodenal adenoma.

To partly answer this question, the spatial position of Paneth cells within the profile of histological sections in duodenal adenomas was recorded.
Materials and Methods

Six endoscopically removed duodenal adenomas found in patients with familial adenomatous polyposis (FAP), were investigated. Sections were stained with hematoxylin and eosin (H&E) in the 6 adenomas and immunohistochemically with lysozyme (DAKO, Glinstrup, Denmark) in 2 of them. The numbers of Paneth cells was assessed in the most populated field in H&E and in lysozyme immnostained sections, using 40x magnifications.

Results

In H&E-stained sections from the 6 adenomas, the numbers of mature Paneth cells/high power field varied from 2 to 7 (mean 4.5). In the two immunostained adenomas, the numbers of lysozyme-expressing cells/high power field were 15 and 42, respectively (Figure 1).

Discussion

In histological H&E-stained sections, the presence of large eosinophilic cytoplasmic granules is the single most important parameter that distinguishes mature Paneth cells. Similar eosinophilic granules are not evident in Paneth cell precursors (9). Since not all the Paneth cells detected by lysozyme immunostain are apparent in consecutive H&E-stained sections (11-16), it is proposed that two histological-immunohistochemical subtypes of Paneth cells can be distinguished: one histologically+ -imunohistochemically+ and the other histologically− -immunohistochemically−. The latter modality seems to detect Paneth cell precursors, cells that remain morphologically undetected in H&E-stained sections.

In the small intestine of mice, the development and epithelial differentiation (including Paneth cells) is under the control of at least three signalling pathways known as Notch, Wnt and hedgehog (5, 6). Recently, Varnat et al. (9) demonstrated that peroxisome proliferator receptor β (PPARβ) a nuclear receptor hormone in the GI tract, is expressed at the bottom of the crypts where Paneth cells reside. PPARβ influences Paneth cell homeostasis by down-regulating the expression of the Indian hedgehog (ihh), a signal sent by mature Paneth cells to regulate the differentiation of Paneth cell precursors (9). From these studies it became apparent that several well-controlled molecular signals regulate mature Paneth cells and their precursors.

Theoretically, one of the possibilities is that lysozyme-stained mature Paneth cells and their precursors are arranged with a certain degree of periodicity in relationship to dysplastic enterocytes, goblet cells and stem cells. However, the lysozyme-stained cells were found haphazardly distributed in different adenoma areas. It would thus appear that mutated stem cells in duodenal adenomas generate dysplastic epithelial cells (including Paneth cells) in a disorderly fashion, thus bypassing the laws that prevail under normal conditions, namely stem cell-to-luminal migration for absorptive enterocytes, goblet cells, enteroendocrine cells on the one hand and stem cell-to-bottom of the crypt migration for Paneth cells on the other (5-9).

Since mature Paneth cells and their precursors are positioned underneath the stem cells, it is conceivable that the Paneth cells that had reached the luminal aspect of the adenomas, were preceded by stem cells. This possibility would imply that in duodenal adenomas, the stem cells would be subjected to the same laws that orchestrate the turnover of epithelial duodenal cells, including Paneth cells and their precursors.

References


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