# Paneth Cells in Colonic Adenomas

## *Association With Male Sex and Adenoma Burden*

*Rish K. Pai, MD, PhD,* Lisa A. Rybicki, MS,† John R. Goldblum, MD,* Bo Shen, MD,‡ Shu-Yuan Xiao, MD,§ and Xiuli Liu, MD, PhD**

**Abstract:** Paneth cells have been reported in colorectal adenomas and adenocarcinomas; however, the frequency of colonic Paneth cell-containing adenomas is unknown as are their clinicopathologic features. A total of 152 consecutive colorectal adenomas from 103 patients (57 males and 46 females) were reviewed. The frequency of Paneth cells in this cohort of adenomas was determined and correlated with patient demographics. Twenty-six adenomas (17.1%) from 22 (21.4%) patients harbored Paneth cells, which were not limited to the base of the crypts but aberrantly located throughout the crypts. Patient age, adenoma size, villous features, and grade of dysplasia were not different between these 2 groups. Not surprisingly, Paneth cell-containing adenomas were more likely to occur in the proximal colon (84.6% vs. 55.6%; $P = 0.006$). There was a strong association between male sex and Paneth cell-containing adenomas, as 23 of 26 (88.5%) of these adenomas occurred in male individuals compared with 71 of 126 (56.3%) non–Paneth cell-containing adenomas ($P = 0.002$). Upon review of an additional 460 adenomas from 200 patients with varying numbers of adenomas (68 with 1 adenoma, 68 with 2 adenomas, and 64 with 3 or more adenomas), the risk of harboring synchronous adenomas was associated with villous morphology, proximal location, and the presence of a Paneth cell-containing adenoma. Thus, the presence of a Paneth cell-containing adenoma may be a marker for increased risk of developing colorectal neoplasia.

**Key Words:** Paneth cells, adenoma, colorectal cancer

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The Paneth cell was first identified by Schwalbe in 1872 and was later studied in detail by Paneth.[1,2] Paneth cells are a component of the innate immune system and elaborate a wide variety of antimicrobial products including defensins.[3] Its differentiation and function are regulated by the APC/Wnt/β-catenin pathway.[3–5] Paneth cells are normally present at the base of the Lieberkuhn crypt in the small bowel, the appendix, and cecum and may be found all the way to the mid transverse colon.[6] Several studies have demonstrated the aberrant presence of Paneth cells in many inflammatory conditions of the colon including inflammatory bowel disease (IBD).[6]

The frequency of Paneth cell-containing adenomas varies widely between studies ranging from 0.2 to 39%.[7–10] In most studies Paneth cell-containing adenomas were more likely to be located in the proximal colon.[8,9,11] There are also some environmental differences on the frequency of Paneth cell-containing adenomas as they are more common in Japanese descendants and white residents in Hawaii than in native Japanese.[8] Paneth cell adenomas may also represent a specific pathway of colorectal carcinogenesis, as a recent study found that all Paneth cell adenomas demonstrated nuclear β-catenin, suggesting activation of the APC/β-catenin pathway.[11] This is not particularly surprising as regulation of normal Paneth cell development is through activation of this pathway.

Although Paneth cells in adenomas have been recognized for some time, there has been no large study that has evaluated the clinical and pathologic features of Paneth cells in adenomas. The aims of the current study are to determine, in a series of colorectal adenomas consecutively diagnosed in US patients, the frequency and distribution of Paneth cell-containing adenomas and their clinicopathologic features. Furthermore, in an additional set of patients with varying numbers of adenomas, we determined whether the presence of a Paneth cell-containing adenoma indicates an increased risk of synchronous colorectal adenomas.

## MATERIALS AND METHODS

### Study Population and Pathologic Evaluation of Colorectal Adenomas

Two retrospective cohorts were identified for this study. The first cohort consisted of 152 colorectal adenomas from 103 patients diagnosed consecutively during a 1-month period in a large medical center in the United States. The second cohort consisted of 200 patients with 1, 2, or more than 3 adenomas in order to determine the

From the Departments of *Anatomic Pathology; †Quantitative Health Sciences; ‡Gastroenterology, Cleveland Clinic, Cleveland, OH; and §Department of Pathology, The University of Chicago Medical Center, Chicago, IL.

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Correspondence: Rish K. Pai, MD, PhD, Department of Anatomic Pathology, Cleveland Clinic, 9500 Euclid Avenue/L25, Cleveland, OH 44195 (e-mail: pair@ccf.org)

relationship between Paneth cell-containing adenomas and adenoma burden. Within this group of patients, 68 had 1 adenoma, 68 had 2 adenomas, and 64 had 3 or more adenomas. Care was taken to have a relatively equal number of patients within each group for statistical analysis. Within each group, the patients were diagnosed consecutively.

In all patients, the purpose of endoscopic evaluation was for screening. Only 1 patient had abdominal pain and diarrhea at the time of colonoscopy, but random biopsies were histologically unremarkable, and therefore this case was included in the study. All patients had their entire colon examined and all of their polyps removed during the endoscopic procedure; all polyps removed were submitted for histologic examination. None of the remaining patients had a clinical history of chronic colitis, including idiopathic IBD, or symptoms of abdominal pain or diarrhea at the time of colonoscopy. None of the patients had a clinical history of familial adenomatous polyposis syndrome. One patient had a history of colonic cancer in her right colon. All adenomas were obtained from endoscopic resections (polypectomy) and rarely endoscopic biopsies for individual polyps. The specimens were fixed in 10% buffered formalin solution, embedded in paraffin, cut into 5-μm-thick sections, and stained with hematoxylin and eosin.

All adenomas were reviewed by 2 gastrointestinal pathologists (R.K.P. and X.L.). On the basis of the percentage of tubular or villous component, the adenomas were diagnosed as either tubular adenoma (> 75% tubular architecture), tubulovillous adenoma (between 25% and 75% for each component), or villous adenoma (> 75% villous architecture).[12] On the basis of the cytologic and architectural features, the adenoma was determined to be low grade or high grade.[12] The specimens were evaluated for the presence and distribution of Paneth cells in the adenomatous tubules. Paneth cells were readily recognized by means of routine hematoxylin and eosin staining, as it contained large, eosinophilic cytoplasmic granules. A Paneth cell-containing adenoma was defined as the presence of a convincingly dysplastic Paneth cell(s) in adenomatous crypts. The presence of Paneth cells in locations other than the base of the crypt was considered an aberrant distribution pattern.

The patient demographics were obtained by reviewing electronic medical records. The location of the adenoma was based on the information provided by the endoscopist. The size of the adenoma was either based on the information provided by the endoscopist or measured from the histology section whenever there was a discrepancy. The adenoma was considered proximal if it was located at or proximal to the splenic flexure and distal if distal to the splenic flexure.

This study has been approved by the institutional review board at Cleveland Clinic.

## Statistical Analysis

Clinicopathologic characteristics were compared between adenomas from male and female patients and between adenomas with and without Paneth cells using either the $\chi^2$ test or Wilcoxon rank sum test. Risk factors for Paneth cell adenomas were assessed using logistic regression analysis. Stepwise logistic regression analysis with a variable entry criterion of $P < 0.10$ and a variable retention criterion of $P < 0.05$ was used to identify multivariable risk factors. Risk factors for polyp burden were determined using 2 methods: ordinal logistic regression to model the risk of 1 versus 2 versus 3+ polyps and logistic regression to model the risk of 1 or 2 versus 3+ polyps. Each analysis included 7 variables as potential risk factors: age, sex, type of adenoma, grade of dysplasia, location, size, and the presence of a Paneth cell adenoma.

**TABLE 1.** Demographics and Adenoma Characteristics of 152 Adenomas From 103 Consecutive Patients

| | Male (N = 57) | Female (N = 46) | *P* |
|---|---|---|---|
| No. adenomas (%) | 94 (61.8) | 58 (38.2) | NA |
| Age* (mean, SD) (y) | 62, 11 | 63, 12 | 0.75 |
| Size (mean, SD) (cm) | 0.6, 0.40 | 0.7, 0.53 | 0.76 |
| Villous features (%) | 7 (7.4) | 2 (3.4) | 0.31 |
| High-grade dysplasia (%) | 4 (4.3) | 2 (3.4) | 0.80 |
| Proximal location† (%) | 56 (59.6) | 36 (62.1) | 0.76 |

*For age 103 patients have been considered; for all other characteristics 152 adenomas have been considered.
†Proximal: from the cecum to splenic flexure (including splenic flexure).
NA indicates not applicable.

# RESULTS

## Clinicopathologic Associations With Paneth Cell-containing Adenomas

A cohort of 103 consecutive patients with 152 adenomas was evaluated for the presence of Paneth cells to determine the frequency of Paneth cells in adenomas and their clinicopathologic characteristics. Table 1 outlines the characteristics of this cohort of 57 male and 46 female patients. There were no differences in adenoma size, location, villous features, and high-grade dysplasia between male and female patients.

The clinicopathologic characteristics of Paneth cell-containing adenomas are shown in Table 2. The frequency of Paneth cell-containing adenomas in the consecutive cohort of 152 adenomas was 17.1% (26 adenomas in 22 patients; 21.4% of all patients). Within the

**TABLE 2.** Characteristics of Paneth Cell Adenomas

| | PCA (n = 26) | Non-PCA (n = 126) | *P* |
|---|---|---|---|
| Frequency (%) | 17.1 | 82.9 | NA |
| Male (%) | 88.5 | 56.3 | 0.002 |
| Median size (cm) | 0.60 | 0.50 | 0.09 |
| Villous (%) | 11.5 | 4.8 | 0.18 |
| HGD (%) | 3.8 | 4.0 | 0.98 |
| Proximal location (%) | 84.6 | 55.6 | 0.006 |

HGD indicates high-grade dysplasia; PCA, Paneth cell adenomas.

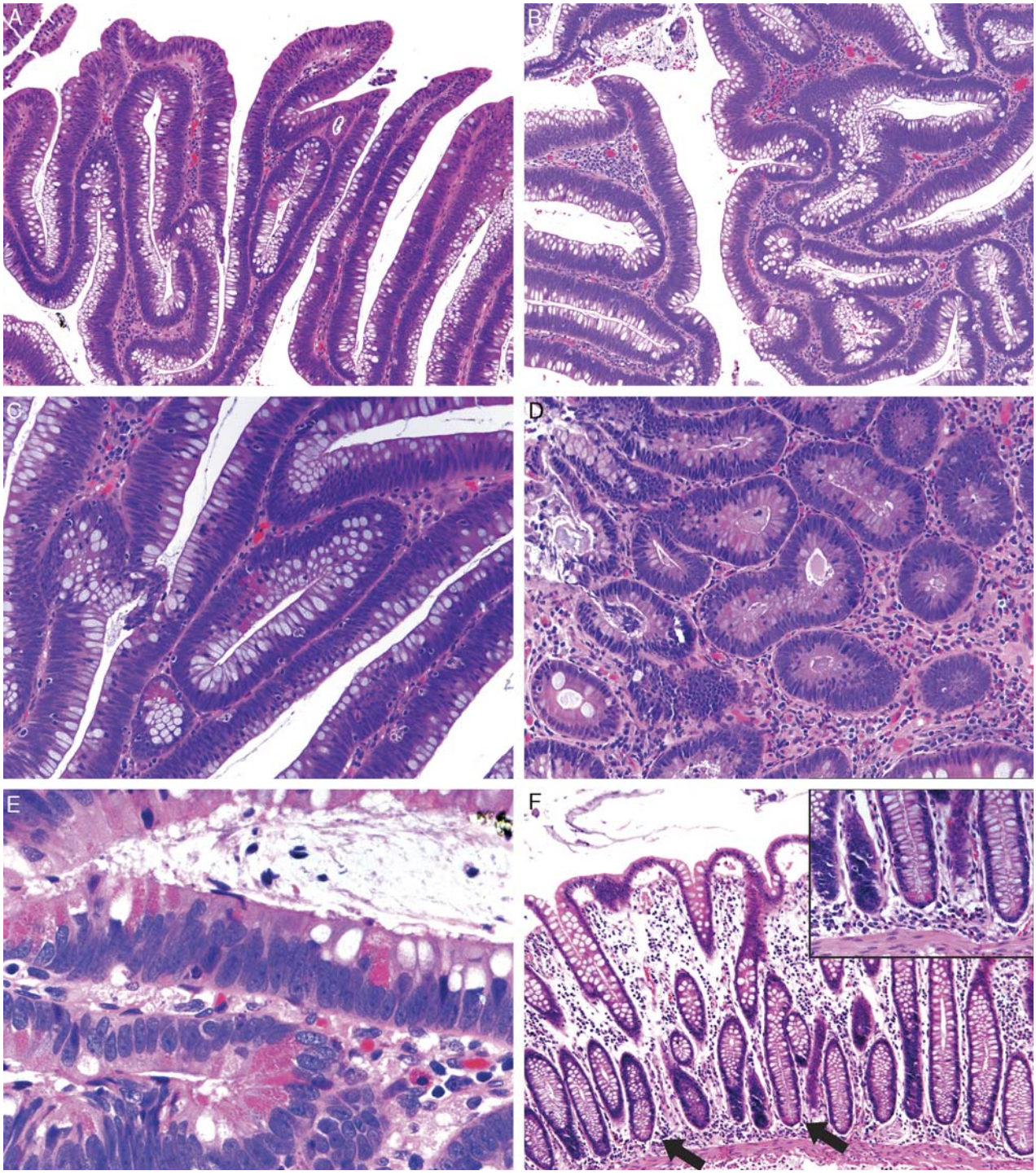


**FIGURE 1.** Histologic features of Paneth cell-containing adenomas. A and B, The Paneth cells within adenomas tended to be located haphazardly within the polyp. The majority of them were not located at the base of the dysplastic crypts. C, In some adenomas Paneth cells were clustered together. D, In other adenomas, Paneth cells had a more dispersed pattern. E, In all cases the Paneth cells within adenomas demonstrated dysplastic nuclear features characterized by stratification and hyperchromasia. F, Typical location and morphology of Paneth cells in non-neoplastic crypts as shown by the arrows. The inset shows a higher power of non-neoplastic Paneth cells located in the crypt bases.

**TABLE 3.** Descriptive Information for the Cohort of 200 Patients With 460 Adenomas

| | N | Percentage (%) |
|---|---|---|
| Age | | |
| Mean | 63 ± 11 | NA |
| Median (range) | 64 (30-86) | NA |
| Male sex | 128 | 64.0 |
| Patients with adenomas with villous features | 24 | 12.0 |
| Patients with adenomas with high-grade dysplasia | 15 | 7.5 |
| Patients with proximal adenomas | 155 | 77.5 |
| Patients with adenoma >1 cm | 64 | 32.0 |
| Patients with a Paneth cell adenoma | 69 | 34.5 |

NA indicates not applicable.

Paneth cell-containing adenomas, Paneth cells demonstrated an aberrant distribution in 97% cases. More specifically, the Paneth cells were usually present in clusters or scattered randomly, in the mid or upper portion of the neoplastic crypts (Figs. 1A–D). In addition, the nucleus of the Paneth cells in the adenoma had dysplastic features similar to their adjacent adenomatous nuclei (Fig. 1E). This is in contrast to the distribution at the base of the crypt seen in normal mucosa and the inconspicuous appearance of Paneth cells in the non-neoplastic glands (Fig. 1F).

The clinicopathologic characteristics of Paneth cell-containing adenomas are shown in Table 2. The majority of Paneth cell-containing adenomas were located in the proximal colon compared with non–Paneth cell-containing adenomas (84.6% vs. 55.6%; $P = 0.006$). Paneth cell-containing adenomas were also much more likely to occur in male individuals (88.5% vs. 56.3%; $P = 0.002$). There was no difference in other pathologic or clinical characteristics between adenomas with and without Paneth cells.

## Patients With Paneth Cell-containing Polyps Have a Higher Polyp Burden

On the basis of analysis of the cohort of 103 patients there was a suggestion that the presence of a Paneth cell-containing adenoma was associated with the presence of increased polyp burden; however, the number of patients with multiple polyps was insufficient to be certain. For this reason another cohort of patients stratified by the number of adenomas was identified. This cohort consisted of 68 patients with 1 adenoma, 68 with 2 adenomas, and 64 with 3 or more adenomas. This cohort of 200 patients had 460 adenomas. All adenomas were reviewed, and the following features were recorded: size, grade of dysplasia, villosity, and the presence of Paneth cells. The characteristics in this cohort of patients are shown in Table 3.

Univariate and multivariate logistic regression analysis was then performed to determine the risk factors for polyp burden. This was done in 2 ways: using ordinal logistic regression to model the risk of 1 versus 2 versus 3+ adenomas and using logistic regression to model the risk of 1 or 2 versus 3+ adenomas. As shown in Table 4, male sex, villous features, proximal location, and presence of a Paneth cell-containing adenoma were associated with the progression from 1 versus 2 versus 3+ adenomas in univariate and multivariate analysis. As patients with 3 or more polyps are screened at a shorter interval, a separate analysis was performed to determine the features associated with 3 or more adenomas. Only 3 factors were associated with 3 or more polyps in univariate and multivariate analysis: villous features, proximal location, and presence of a Paneth cell-containing adenoma. Male sex, adenoma size, and grade of dysplasia were not associated with 3 or more adenomas.

## DISCUSSION

Paneth cells, a normal constituent of the small bowel, appendix, and proximal colon, play a significant role in innate intestinal immunity.[3] Dysfunction and dysregulation of Paneth cells have been implicated in the development of idiopathic IBD,[3] and Paneth cell metaplasia in the distal portion of the colon is a known morphologic phenomenon in patients with IBD and other chronic inflammatory conditions of the large intestine.[6] The incidence of Paneth cells in colorectal neoplasms and its adjacent mucosa has been reported for >4 decades.[6–11,13] In a large study of 5778 adenomas, Paneth cells were seen in only 0.2%.[7] Other studies, predominately from Asia, demonstrated a frequency of Paneth cells in adenomas between 17% and 39%.[8,9,11] Interestingly, there are likely environmental differences in Paneth cell-containing adenomas, as they are more common in

**TABLE 4.** Risk Factors for the Development of Multiple Polyps

| | Odds Ratio (*P*) | | | |
|---|---|---|---|---|
| | 1, 2, or 3+ Polyps | | 3 or More Polyps | |
| Variable | Univariate | Multivariate | Univariate | Multivariate |
| Age, per 10-y increase | 1.15 (0.25) | — | 1.20 (0.21) | — |
| Sex | 2.36 (0.002) | 2.00 (0.019) | 1.68 (0.11) | — |
| Villous features | 2.64 (0.020) | 2.77 (0.018) | 2.90 (0.016) | 3.16 (0.023) |
| High-grade dysplasia | 1.76 (0.26) | — | 1.96 (0.21) | — |
| Proximal location | 4.10 (< 0.001) | 3.03 (0.002) | 30.13 (< 0.001) | 20.56 (0.004) |
| Size >1 cm | 1.63 (0.08) | — | 1.76 (0.07) | — |
| Presence of Paneth cell adenoma | 4.31 (< 0.001) | 2.73 (0.001) | 4.45 (< 0.001) | 3.12 (0.001) |

Japanese descendants and white residents in Hawaii than in native Japanese.[8]

In this study, we found the frequency of Paneth cell-containing adenomas in 152 consecutive adenomas from 103 patients to be 17.1% and 21.4% at the polyp level and the patient level, respectively. These rates are consistent with previous reports, which showed a frequency of 17% to 39% among all polyps, although much higher than those reported by Bansal et al.[7] Our study also confirmed a predilection for the proximal colon, in line with previous observations.[8,9] However, for the first time we report a striking male predominance within our cohort of Paneth cell-containing adenomas. In our cohort, 88.5% of the Paneth cell-containing adenomas occurred in male patients; in contrast, only 56.3% of the non–Paneth cell-containing adenomas occurred in male patients ($P = 0.002$). This finding is in contrast with 2 previous studies reporting a lack of sex differences between Paneth cell-containing and non–Paneth cell-containing adenomas.[8,9] This discrepancy may be due to the different methods used in defining Paneth cell-containing adenoma, different ethnicities in the study population, or different sizes and types of adenoma. Our study defined Paneth cell-containing adenomas as the presence of Paneth cell(s) in adenomatous tubules, and cases with Paneth cells only in the non-neoplastic glands/crypts were considered as non–Paneth cell-containing adenomas. Furthermore, our study included a series of consecutively diagnosed adenomas including tubular, tubulovillous, and villous adenomas, and the study population was mainly composed of white patients from the United States. In contrast, the lack of relationship between patient sex and the incidence of Paneth cells in the adenomas reported in 2 studies by Wada et al[8,9] was based on 2 series of tubular adenomas predominantly from either native Japanese or Japanese descendants in Hawaii and in tubular adenomas < 5 or 10 mm in diameter. Also, no detailed information was provided on the definition of Paneth cell-containing adenomas in those 2 studies.

As Paneth cells are normally seen in the proximal colon, it is reasonable to expect a higher incidence of Paneth cell-containing adenomas in this segment. It is also possible that some of these Paneth cells represent entrapped non-neoplastic cells. However, the aberrant distribution of Paneth cells within the adenomas differs from their basal location in normal crypts. In some cases, Paneth cells in the neoplastic crypts tended to cluster and, sometimes, occupy almost the entire length of crypts. Furthermore, the nuclei of the Paneth cells within the adenomatous tubules had features of dysplasia. These 3 features support that Paneth cells are a part of the neoplastic component of the adenoma. The male preponderance of this phenomenon suggests that it is not a "random" change in the neoplastic transformation. It remains unknown why Paneth cell-containing adenomas are predominantly found in the proximal colon in male patients. The microenvironment in the proximal colon of male patients and possibly differences in sex hormones may be contributory factors. Review of the distribution of Paneth cells in the colon of normal male and female patients may help resolve this issue.

Finally, in an analysis of 460 polyps from 200 patients we found that the presence of a Paneth cell-containing adenoma is associated with increased polyp burden. In multivariate analysis, villous features and proximal location were also associated with increased polyp burden. Villous features, high-grade dysplasia, and large size have all been associated with increased risk of synchronous adenomas.[14,15] These features along with having 3 or more adenomas and proximal adenomas also increase the risk of adenoma recurrence in subsequent colonoscopies.[16–19] Patients with large serrated polyps also have an increased risk for synchronous adenomas.[20–22] Our study describes for the first time the risk of synchronous neoplasia in patients with a Paneth cell-containing adenoma (odds ratio of 3.12 for 3 or more polyps). One could argue that the association between the presence of a Paneth cell-containing adenoma and synchronous adenomas is simply due to chance, as the greater number of polyps a patient has, there exists an increased likelihood of having an adenoma with Paneth cells. This would be true if the presence or absence of Paneth cells within adenomas is a random event; however, this is clearly not the case given the strong association with proximal location and male sex. This finding suggests that the presence of Paneth cell-containing adenoma may indicate a predisposition to colorectal tumorigenesis.

Recent studies have shown that the differentiation and function of Paneth cells are tightly regulated by the APC/Wnt/β-catenin pathway,[3–5,23] a pathway known to be altered during colorectal tumorigenesis.[24,25] In line with these findings from basic research, the high incidence of Paneth cells (up to 43%) was noted in familial adenomatous polyposis–associated adenomas located in the cecum.[26] A recent study by Joo et al[11] also demonstrated that 100% of Paneth cell-containing adenomas demonstrated β-catenin activation compared with only 66% of adenomas without Paneth cells. These data indicate that Paneth cells within an adenoma is a morphologic marker of activation of the APC/Wnt/β-catenin pathway; that is, activation of β-catenin, a key regulator of the fate of Paneth cells, and activation of Tcf4, a key regulator of Paneth cell function. Taken together, these results suggest that the presence of a Paneth cell-containing adenoma identifies patients with an increased risk of developing colorectal adenomas.

## REFERENCES

1. Paneth J. Uber die secernierenden Zellen des Dunndarm-Epithels. *Arch Mikroskop Anat*. 1888;31:113–191.
2. Schwalbe G. Beitrage zur enntniss der Drusen in den Dramwanddungen in's Besondere Brunnerschen Drusen. *Arch Mikroskop Anat*. 1872;8:92–140.
3. Salzman NH, Underwood MA, Bevins CL. Paneth cells, defensins, and the commensal microbiota: a hypothesis on intimate interplay at the intestinal mucosa. *Semin Immunol*. 2007;19:70–83.
4. Andreu P, Peignon G, Slomianny C, et al. A genetic study of the role of the Wnt/beta-catenin signalling in Paneth cell differentiation. *Dev Biol*. 2008;324:288–296.

5. Chen X, Ehrhardt WM, Halberg RB, et al. Cellular expression patterns of genes upregulated in murine and human colonic neoplasms. *J Histochem Cytochem*. 2008;56:433–441.
6. Symonds DA. Paneth cell metaplasia in diseases of the colon and rectum. *Arch Pathol*. 1974;97:343–347.
7. Bansal M, Fenoglio CM, Robboy SJ, et al. Are metaplasias in colorectal adenomas truly metaplasias? *Am J Pathol*. 1984;115:253–265.
8. Wada R, Kuwabara N, Suda K. Incidence of Paneth cells in colorectal adenomas of Japanese descendants in Hawaii. *J Gastroenterol Hepatol*. 1994;9:286–288.
9. Wada R, Miwa H, Abe H, et al. Incidence of Paneth cells in minute tubular adenomas and adenocarcinomas of the large bowel. *Acta Pathol Jpn*. 1992;42:579–584.
10. Wada R, Yamaguchi T, Tadokoro K. Colonic Paneth cell metaplasia is pre-neoplastic condition of colonic cancer or not? *J Carcinog*. 2005;4:5.
11. Joo M, Shahsafaei A, Odze RD. Paneth cell differentiation in colonic epithelial neoplasms: evidence for the role of the Apc/beta-catenin/Tcf pathway. *Hum Pathol*. 2009;40:872–880.
12. Hamilton SR, Bosman FT, Bofetta P, et al. Carcinoma of the colon and rectum. In: Bosman FT, Carneiro F, Hruban RH, eds. *WHO Classification of Tumors of the Digestive System*. Lyon, France: International Agency for Research on Cancer; 2010:134–146.
13. Holmes EJ. Neoplastic Paneth cells; their occurrence in 2 adenomas and one carcinoma of the colon. *Cancer*. 1965;18:1416–1422.
14. Chung YW, Han DS, Park YK, et al. Risk of advanced proximal adenoma and cancer according to rectosigmoid findings in the Korean population. *Dig Dis Sci*. 2006;51:2206–2212.
15. Papatheodoridis GV, Triantafyllou K, Tzouvala M, et al. Characteristics of rectosigmoid adenomas as predictors of synchronous advanced proximal colon neoplasms. *Am J Gastroenterol*. 1996;91:1809–1813.
16. Bonithon-Kopp C, Piard F, Fenger C, et al. Colorectal adenoma characteristics as predictors of recurrence. *Dis Colon Rectum*. 2004;47:323–333.
17. Martínez ME, Baron JA, Lieberman DA, et al. A pooled analysis of advanced colorectal neoplasia diagnoses after colonoscopic polypectomy. *Gastroenterology*. 2009;136:832–841.
18. van Stolk RU, Beck GJ, Baron JA, et al. Adenoma characteristics at first colonoscopy as predictors of adenoma recurrence and characteristics at follow-up. The Polyp Prevention Study Group. *Gastroenterology*. 1998;115:13–18.
19. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *Gastroenterology*. 2006;130:1872–1885.
20. Mattar W, Rex DK. Large sessile adenomas are associated with a high frequency of synchronous advanced adenomas. *Clin Gastroenterol Hepatol*. 2008;6:877–879.
21. Li D, Jin C, McCulloch C, et al. Association of large serrated polyps with synchronous advanced colorectal neoplasia. *Am J Gastroenterol*. 2009;104:695–702.
22. Vu HT, Lopez R, Bennett A, et al. Individuals with sessile serrated polyps express an aggressive colorectal phenotype. *Dis Colon Rectum*. 2011;54:1216–1223.
23. Husøy T, Ølstørn HB, Knutsen HK, et al. Truncated mouse adenomatous polyposis coli reduces connexin32 content and increases matrilysin secretion from Paneth cells. *Eur J Cancer*. 2004;40:1599–1603.
24. Dove WF, Cormier RT, Gould KA, et al. The intestinal epithelium and its neoplasms: genetic, cellular and tissue interactions. *Philos Trans R Soc Lond B Biol Sci*. 1998;353:915–923.
25. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic alterations during colorectal-tumor development. *N Engl J Med*. 1988;319:525–532.
26. Iwama T, Utsunomiya J, Hamaguchi E. The Paneth cell in the adenoma of familial polyposis coli. *Bull Tokyo Med Dent Univ*. 1975;22:151–154.

 