Letter to the editor

Initial transformed cells of colorectal adenoma: do they occur at the top of the crypt?

To the Editor. In the large intestine, there is general agreement that stem cells exist at the base of the crypt, and that dysplastic cells originate in a single abnormal precursor stem cell. Thus, it is generally thought that buds of single-gland adenomas arise from the base of the crypt, and then move upward with migration of the epithelial cells of the crypt. In small colorectal adenomas, however, two-layer structures with dysplastic epithelial cells in the upper part of the crypt, and normal-appearing epithelial cells in the lower part of the same crypt, are often observed histologically.

Recently, le-Ming Shih et al. presented an article entitled “Top-down morphogenesis of colorectal tumors”. To understand the above-described discrepancy, they evaluated the molecular characteristics of cells isolated from the bases and tops of the same crypts in small colorectal adenomas. They showed that dysplastic cells at the tops of the crypts contained genetic alterations of the adenomatous polyposis coli (APC) gene at the high rate of 90%, and that, in contrast, cells located at the bases of these same crypts appeared normal morphologically, and did not have such genetic alterations. They also found that none of the crypts were lined by uniformly dysplastic cells throughout their length. In the discussion section of their article, they emphasized that the dysplastic process proceeds from the top down rather than from the bottom up. They envisioned one possible explanation for their idea of top-down morphogenesis (as shown in Fig. 6B of their original article), which was that the precursors of the dysplastic cells would actually reside in the intercryptal zones on the surface of the mucosa rather than at the bases of the crypts.

As previously reported, we investigated the surface structure of normal colonic mucosa and small adenoma by scanning electron microscopy. In normal colonic mucosa, a round orifice was observed in the center of the crypt, and the surrounding border of the crypt, which looked like a pentagonal ditch, was clearly observed (Fig. 1). On the other hand, in small adenoma, the orifice of the crypt was deformed into an elongated tubular shape, and dysplastic epithelium spread laterally, pushing aside the normal epithelium. Thus, the border of the crypt was irregular, with a wormeaten like appearance (Fig. 2). In our histological examinations of small adenomas in hematoxylin-and-eosin-stained serial sections, we observed transitions between dysplastic and normal epithelium in the same crypt, which existed at the edge of the adenoma, and we named these transitional points “demarcation points”. Thus, these findings were similar to those reported by le-Ming Shih et al. However, we cannot agree with their argument that the precursors of the dysplastic cells would reside on the surface of the mucosa, because we found that, in adenoma, some crypts were lined by dysplastic cells from the top to the base of the crypt. We think that dysplastic cells originate at the base of the normal crypt and initially migrate up the crypt, and then spread laterally and downward to the adjacent crypts along the basement membrane, and form the demarcation points by replacing the normal cells from the upper part of the adjacent crypts (Fig. 3).

In conclusion, le-Ming Shih et al. showed important evidence that the normal-appearing epithelial cells at the base of the crypt in small adenomas were normal genetically as well as morphologically. However, we think that their attractive theory, of top-down morphogenesis, is not so persuasive as to disprove the conventional theory that the transformation of a single epithelial cell occurs at the base of the crypt initially.
Fig. 1. a Scanning electron microscopic findings of normal surface of the colon. Round orifices were observed in the centers of crypts, and the surrounding border of the crypt, which looked like a pentagonal ditch, was clearly observed. b High power scanning electron microscope view of a. a ×300; b ×600

Fig. 2. a Scanning electron microscopic findings of colorectal adenoma. The orifices of the crypt were deformed into an elongated tubular shape. b The border of the crypt had become irregular, with a wormeaten like appearance. a ×500; b ×250