Possible Mechanism Pertinent to Mucosal Invasion in Sporadic Colonic Adenomas

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Abstract. Colorectal adenomas are foci of dysplastic mucosa that may antedate the development of a colorectal cancer. In this work we investigated 62 colonic polyps. A close examination revealed that in some adenomatous glands facing the muscularis mucosa a group of dysplastic cells were missing. Those glandular defects were connoted as glandular pores. Many glands with pores were dilated and had retained mucin, inflammatory cells and/or necrotic material. Those products were often released through the pores into the surrounding lamina propria. Glandular pores were recorded in 25% (3/12) of the tubular adenomas, in 33% (2/6) of the serrated adenomas, in 50% (4/8) of the tubulo-villous adenomas and in 67% (14/21) of the villous adenomas. None of the 14 hyperplastic polyps had glandular pores. While cell locomotion is considered to be the most important parameter accountable for the local progression of tumors, the present results may offer an alternative view to the cell-migration theory (as the sole pathway of invasion). The release of proteolytic secretions through glandular pores in some colonic adenomas disrupt the surrounding matrix, a mechanism that would facilitate neoplastic cell penetration into the lamina propria.

Colorectal adenomas are foci of dysplastic mucosa that may antedate the development of colorectal cancer. Invasion occurs when a dysplastic cell acquires properties that enable it to penetrate the surrounding tissue or basement matrix and establish growing masses within normal tissues (1). However, the dysplastic cells in adenomas seem to have low invasive properties. Muto et al. (2) claimed that most adenomas do not become cancerous during a normal adult life span and Williams and Bedenne (3) reported that fewer than 10% of colorectal adenomas evolve into invasive carcinoma. Such a low percent of malignant transformation is remarkable considering that adenomas are engaged in intense cell proliferation, as deduced from Ki67 immunostain trials (4). Thus, a high proliferation rate per se does not trigger stromal invasion.

Among the questions that remain concerning the mechanism(s) involved in the initial host invasion are: why do dysplastic cells acquire the property to invade the basement matrix of the host? and, once that acquired property has been achieved: How does invasion take place? To gain information about the steps required for host invasion, several microscopic and molecular parameters have been investigated such as cell proliferation (5), mitotic rate (6,7), E-cadherin, beta-catenin (8) and neoangiogenesis (9). It has been claimed that the ability of dysplastic cells to acquire invasive properties may be related to gene mutations of the Tp53 protein (10,11). However, as that protein is found in only 50% of colorectal adenomas and carcinomas other parameters may be involved, at least in the remaining neoplasias. Nevertheless, despite extensive literature on morphologic and molecular events, the questions of why and how glands furnished with dysplastic cells become committed to invade through the basement matrix have not been fully answered.

Recently, while investigating the growing edge of invasive sporadic colorectal carcinomas (12,13), of colorectal carcinomas in inflammatory bowel disease (14) and in experimental colorectal adenocarcinomas in rats (15), we found that the invasive neoplastic glands lacked a group of tumor cells. This lack of cells in neoplastic glands was referred to as glandular pores. Through these pores mucins, inflammatory cells and/or necrotic material were released directly into the juxtaposed extracellular matrix (ECM). These secretions, rich in proteolytic enzymes (16), disrupt the ECM. It was suggested that malignant cells proliferating from the tip of the glandular pores invaded the disrupted matrix, a mechanism that would guarantee a stepwise, but everlasting tumor progression in untreated patients. The results of those investigations suggested that, in overt
colorectal adenocarcinomas, an enzymatic mechanism may precede cellular invasion.

More recently, while reviewing colonic adenomas (17), we noticed that some of the dysplastic glands facing the basement membrane also had glandular pores. The purpose of this study was to investigate the frequency of glandular pores in a cohort of colonic polyps.

Materials and Methods

Histological sections from 62 colonic polyps were reviewed. The sections were stained with hematoxylin and eosin (H & E). The polyps were histologically divided into hyperplastic (non-neoplastic) and neoplastic (i.e. adenomas). Adenomas (without invasive growth into the lamina propria or into the submucosa) were histologically classified into tubular, villous, mixed (tubulo-villous) and serrated. Hyperplastic (metaplastic) polyps were considered to be those foci of hyperplastic non-neoplastic mucosa in which the Lieberkühn’s crypts had sawtooth configuration due to crenate epithelium. Tubular adenomas were considered to be lesions having ≥80% dysplastic tubuli. Tubuli are closely packed, transversally cut, dysplastic colonic crypts. Villous adenomas were regarded to be lesions having ≥80% dysplastic villous fronds. Villi are in reality the sides of elongated, hyperplastic crypts of Lieberkühn.

Of the 62 colonic polyps, 14 were hyperplastic, 12 were tubular, 21 villous, 8 mixed and 6 serrated adenomas.

Pore formation was defined as a glandular defect consisting of a lack of a group of dysplastic cells in the deeper portion of the glands or crypts.

Results

Of the 12 tubular adenomas, three (25%) had glandular pores (Figure 1). Fourteen of the 21 villous adenomas (66.7%) had pore formations. Pore formation in villous adenomas occurred at the base of the crypts (Figure 2). Of the 8 tubulo-villous adenomas, 4 (50%) had glandular pores and, from the 6 serrated adenomas, 2 (33%) had glandular pores in the dysplastic crypts.

Dysplastic glands with pores were usually dilated and showed retained mucins, inflammatory cells and/or necrotic material (Figure 2).

None of the crypts in the 14 hyperplastic polyps had glandular pores.

Discussion

In previous studies (12-15) we found, at the invading front of colorectal adenocarcinomas, that some of the neoplastic glands were dilated and contained retained material. That material – rich in proteolytic enzymes (16) – was seen released directly into the extracellular matrix (ECM) and resulted in the disruption of the juxtatumoral ECM. It was suggested that malignant cells, proliferating from the tip of the glandular pores, invaded the disrupted ECM. The growth of new cancer cells into that disrupted matrix would guarantee a stepwise but everlasting tumor progression in untreated patients.
The present investigation (comprising colonic adenomas without invasive growth into the lamina propria or into the submucosa) showed that 37% (or 23 out of 62) of the sporadic colonic polyps had dysplastic glands with one or more epithelial pores. Whereas none of the 14 hyperplastic (non-neoplastic) polyps had pores, 25% of the tubular adenomas, 33% of the serrated adenomas, 50% of the tubulo-villous adenomas and nearly 67% of the villous adenomas had pores in one or more dysplastic glands.

Dysplastic glands with pores were usually dilated due to retained secretions. Those glandular secretions released into the mucosa through the pores induced the disruption of the juxtaposed lamina propria (Figure 2). That phenomenon appeared to be more pronounced in invasive colonic adenocarcinomas (12-15).

It may be argued that pore formation in adenomatous dysplastic glands is a peculiar event. But if that is so, why are pores mainly seen in dysplastic glands facing the muscularis mucosa? Further, why are pores less common in tubular adenomas, i.e. adenomas having a low percent of invasive growth at the time of endoscopic removal (2), than in villous adenomas, i.e. adenomas with a much higher percent of host invasion (2)? Finally, why are they not present in hyperplastic polyps?

If the present findings are confirmed in a larger series of colonic adenomas, it is conceivable that pore formation with released secretions may be a phenomenon that encourages adenomatous cells to a more aggressive behaviour. If that were the case, the rational question is: are adenomas with dilated glands having retained mucins, inflammatory cells and/or necrotic material as well as pores committed to future invasive growth? These questions are receiving particular attention at this Laboratory (18).

Research on the mechanism of tumor invasion has so far been focused on the kinetic ability of cancer cells to migrate into the surrounding matrix (1). While cell locomotion is considered to be the most important parameter accountable for the local progression of tumors (1), the present results may offer an alternative view to the cell-migration theory (as the sole pathway of invasion). The release of proteolytic-rich secretions through glandular pores in some colonic adenomas destabilizes the surrounding connective tissue, a mechanism that would facilitate neoplastic cell penetration into the lamina propria.

References


