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Original contribution

Wnt signaling pathway is activated in right colon serrated polyps correlating to specific molecular form of β-catenin

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Summary The role of the Wnt signaling pathway in the tumorigenesis of sessile serrated adenoma (SSA) of the colorectum remains controversial. Using 2 antibodies targeting different epitopes (C-terminus and N-terminus), β-catenin expression in 35 SSAs and 30 right-sided hyperplastic polyps (RHPs) was examined by immunohistochemistry. Samples of 10 normal colorectal mucosa, 32 left-sided hyperplastic polyps, 27 traditional serrated adenomas (TSAs), and 40 traditional adenomas (TAs) were used as controls. Expression of adenomatous polyposis coli (APC) and mutated in colorectal cancer (MCC), key regulators of β-catenin, was also examined by immunohistochemistry. Using the C-terminus antibody, no nuclear staining of β-catenin was observed in any SSAs or RHPs. However, with the N-terminus antibody, accumulation of β-catenin was seen in 40.0% of SSAs and 33.3% of RHPs. The average immunoreactivity score of APC in SSAs (67.0 ± 21.6) and RHPs (69.2 ± 24.4) was significantly higher than that in TAs (22.0 ± 18.0) and TSAs (49.5 ± 23.1; all $P < .05$). In contrast, MCC was more frequently lost in right-sided-polyps such as SSA and RHP than in left-sided polyps such as left-sided hyperplastic polyp, TSA, and TA. Our results suggest that Wnt signaling is activated in SSA and its possible precursor lesion RHP. The present study also implied that the specific molecular form of β-catenin may participate in the Wnt signaling activation of right-sided serrated polyps. Moreover, loss of MCC expression but not APC may contribute to the early activation of Wnt signaling in right-sided serrated polyps.

1. Introduction

Most colorectal cancers (CRCs) develop through a traditional adenoma (TA)-carcinoma sequence [1,2]. However, recent studies suggest that 10% to 20% of CRCs arise through a "serrated polyp-neoplasia pathway" [3-6]. The recognition of this pathway in recent years has led to a paradigm shift toward thinking of CRC as a genetically heterogeneous disease and to significant changes in clinical practice [7].

Serrated polyps are histologically classified into hyperplastic polyps (HPs), traditional serrated adenomas (TSAs), and sessile serrated adenomas (SSAs) [8,9]. TSAs are characterized by a predilection for the distal colon and rectum, and the subsequent cancer risk rate at least equals that of TAs [10,11]. HPs were further classified into microvesicular (MVHP), goblet cell (GCHP), and mucin-depleted variants [12]. GCHP is located almost exclusively in the left colon, and MVHP is still mainly left sided but with more right-sided lesions than GCHP [13]. HPs are commonly defined as

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benign lesions without neoplastic potential. However, it has been suggested that MVHP (especially right sided) may be a precursor to more advanced SSA [8,13,14].

SSA cytologically resembles HP but is distinguished from HP by larger size, a predominantly right-sided location, and neoplastic potential. Recent studies have revealed that SSAs are high-risk lesions, with 15% of the patients with SSA developing CRCs or adenomas with high-grade dysplasia (HGD), and the neoplastic progression within this pathway is faster than within the classical adenoma-carcinoma sequence [10,15,16]. However, the details of the molecular mechanism of stepwise progression from SSA to early invasive carcinoma remain to be explored.

It's well known that the Wnt signaling pathway involving β-catenin plays a key role in the carcinogenesis of the classical adenoma-carcinoma sequence [17,18]. However, the published results on Wnt signaling activation in SSA are conflicting. Some studies have detected frequent nuclear accumulation of β-catenin in SSAs [19,20], but our previous study and others have suggested that Wnt pathway activation, seen as nuclear labeling for β-catenin, is unlikely to contribute to tumorigenesis in most SSAs [21-24].

β-Catenin is the central and essential component in the canonical Wnt signaling pathway. Previous studies have proposed that cells contain a number of distinct molecular forms of β-catenin at the protein level [25]. For example, there are at least 2 forms of β-catenin with differential selectivity for adhesion and transcription complexes [26].

Activation of the Wnt signaling pathway in CRC occurs always through mutation of adenoma polyposis coli (*APC*) or *CTNNB1* (β-catenin) [27]. Loss of APC function leads to β-catenin translocation into the nucleus, promoting the transcription of multiple genes involved in tumor growth and invasion [28]. Furthermore, recent studies have shown that mutated in CRC (MCC), a candidate tumor suppressor, can also interact with β-catenin and affect endogenous β-catenin levels [29].

In the present study, we examined the expression of β-catenin, APC, and MCC in SSAs and right-sided hyperplastic polyps (RHPs) and compared the findings with normal colorectal mucosa (NCs), left-sided hyperplastic polyps (LHPs), TSAs, and TAs. Because in vivo β-catenin exists in different states (the adhesion and transcriptional complexes with β-catenin binding proteins), the detection of β-catenin with antibodies may be selective. Thus, we used 2 antibodies targeting different epitopes of β-catenin (C-terminus and N-terminus). The goal of our study was to determine the role of the Wnt signaling pathway and its possible regulatory mechanism in serrated polyps of the right colon.

2. Methods

2.1. Sample collection

We identified a total of 164 polyps from the patients who underwent colonoscopic polypectomy in the Affiliated Hospital of Luzhou Medical College during the period of January 2006 to November 2011. All samples were reviewed by the corresponding author and classified as LHPs (n = 32), RHPs (n = 30), SSAs (n = 35), TSAs (n = 27), and TAs (n = 40). Specimens of 10 normal colorectal mucosa (NC) were used as controls. HPs have prominent serrations toward the luminal surface and crypts that narrow toward the muscularis mucosae (Fig. 1A). In contrast, SSAs are characterized by larger size, predilection for proximal colon, abnormal proliferation, basilar crypt distortion, and dilatation toward the muscularis mucosae (Fig. 1B). Clinicopathologic data for each patient were obtained from hospital records. Polyp size

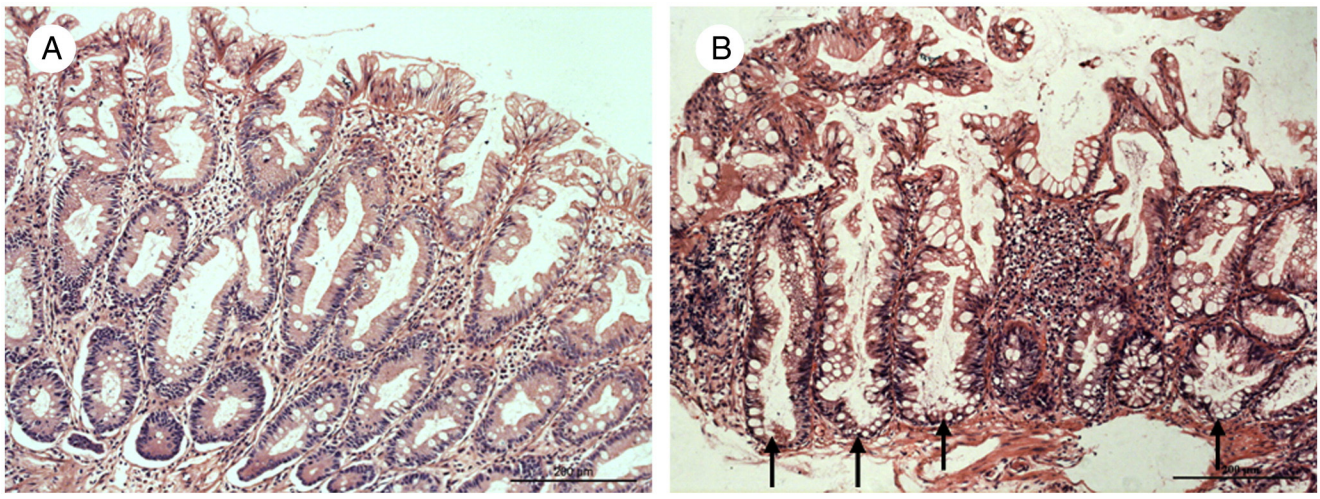

Fig. 1 Histologic features of serrated polyps. A, Hyperplastic polyp: the serrations of the epithelium are confined to the upper half of the crypts. B, SSA: in contrast to the hyperplastic polyp shown in panel A, the architecture of the crypts is distorted, seen as basal crypt dilatation (arrows) and crypt branching. Hematoxylin and eosin staining, ×100. Scale bars = 200 μm.