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BRAF and *KRAS* Mutations in Colorectal Hyperplastic Polyps and Serrated Adenomas[1]

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ABSTRACT

Colorectal cancer is believed to progress through an adenoma–carcinoma sequence. However, recent evidence increasingly supports the existence of an alternative route for colorectal carcinogenesis through serrated polyps, a group that encompasses a morphological spectrum, including hyperplastic polyp (HP), admixed hyperplastic polyp/adenoma (HP/AD), and serrated adenoma (SA; the latter two manifest epithelial dysplasia). We have studied a large series of serrated polyps for *BRAF* and *KRAS* mutations. *BRAF* mutations were detected in 18 of 50 (36%) HPs, 2 of 10 (20%) HP/ADs, and 9 of 9 (100%) SAs. Twenty-six of 29 mutations caused amino acid substitutions at valine 599, the known hotspot. *KRAS* mutations were detected in 9 of 50 (18%) HPs, 6 of 10 (60%) HP/ADs, and 0 of 9 (0%) SAs. *BRAF* and *KRAS* mutations are mutually exclusive ($P = 0.001$). The associations of *BRAF* mutations with SAs ($P < 0.001$) and *KRAS* mutations with HP/ADs ($P = 0.005$) are statistically significant. A majority (90%) of the serrated polyps showing dysplasia had mutations in either *BRAF* or *KRAS*, significantly different from those without dysplasia (54%; $P = 0.014$). Our data highlight the important role of activation of the RAS-RAF-mitogen-activated protein/extracellular signal-regulated kinase kinase-extracellular signal-regulated kinase-mitogen-activated protein kinase pathway in the initiation and progression of serrated neoplasms. Acquisition of a *BRAF* mutation appears to be associated with the progression of HP to SA, whereas progression to HP/AD is predominantly associated with acquisition of a *KRAS* mutation. The high incidence of *BRAF* mutations in HPs and SAs is consistent with the notion that the group of colorectal cancers carrying *BRAF* mutations may harbor most that have progressed through the HP-SA-carcinoma pathway.

INTRODUCTION

RAS proteins participate in the RAS-RAF-MEK[3]-ERK-MAP kinase pathway, which mediates cellular responses to growth signals (1). Somatic mutations of the *RAS* genes, leading to activation of this signaling pathway and malignant transformation, are common in human cancers. There are three *RAF* genes, each encoding cytoplasmic serine/threonine kinases that are regulated by binding to RAS (1, 2). We have shown previously that mutations of *BRAF* provide an alternative route for activation of this signaling pathway in human cancers (3). *BRAF* mutations can be found in malignant melanoma, colorectal cancers, and ovarian borderline (low malignant potential) tumors, and they tend to occur in a mutually exclusive relationship with *RAS* mutations (3–5). Subsequently, *BRAF* mutations have also been found in most benign melanocytic naevi and lung cancer (6–8). Mutations in *BRAF* occur in two regions of the *BRAF* kinase domain, the activation segment (which protects the substrate binding site), and, less commonly, the G loop (which mediates binding of ATP). Mutated forms of *BRAF* that have been studied thus far have elevated kinase activity and can transform NIH3T3 cells (3).

An adenoma–carcinoma sequence has long been recognized to constitute a major pathway of colorectal carcinogenesis (9). *KRAS* is known to play an important role in the progression along this pathway, predominantly occurring during the transformation of small to intermediate sized adenomas (10). We and others have demonstrated the involvement of *BRAF* in a similar phase of colorectal cancer development, albeit in a much smaller percentage of cases (3–10% of adenomas have *BRAF* mutations compared with ~30–60% with *KRAS* mutations; Refs. 4 and 5). Emerging evidence supports the existence of an alternative pathway of colorectal cancer development through the serrated polyp (for review, see Refs. 11 and 12). The serrated polyp encompasses a morphological spectrum, including HPs, HP/ADs, and SAs. HPs of the large intestine are found in ~12% of individuals >50 years of age (13, 14). Morphologically, they are characterized by elongated crypts with serrated architecture covered by nondysplastic colonic epithelial cells. It has been suggested that HPs arise because of hypermaturation of glandular cells consequent on diminished apoptosis (15), but their pathogenesis and propensity for malignant progression remain controversial. Subsequently, two morphological variants of HPs that are associated with epithelial dysplasia have been recognized. The term SA has been used for polyps with serrated morphology (as seen in ordinary HPs) that show epithelial dysplasia throughout the lesion. HP/ADs show focal hyperplastic and focal adenomatous components (16, 17). Evolution of these lesions to invasive carcinomas has been reported (18–21).

Molecular studies have indicated that serrated polyps (including HPs) are likely to be clonal neoplasms, because mutations of *KRAS* and p53, MSI, and chromosome 1p loss have been found in variable proportions (22–30). However, mutations of adenomatous polyposis coli are uncommon (26, 30, 31). Overall, the molecular pathway of evolution in serrated polyps and its relative contribution to the incidence of colorectal cancer are unclear.

In our recent study of *BRAF* and *KRAS* mutations in colorectal polyps, one of three HPs showed a *BRAF* mutation (4). This finding has prompted us to examine a larger series of serrated polyps for *BRAF* and *KRAS* mutations with reference to their morphological classification, in particular the presence of dysplasia and MSI.

MATERIALS AND METHODS

Materials. Pathology records and histological slides with a diagnosis of either HP, HP/AD, or SA from 1997 to 2002 in the Department of Pathology, Queen Mary Hospital were reviewed independently by two pathologists with an interest in gastrointestinal neoplasia (S. Y. L. and S. T. Y.). Six-μm-thick sections were cut from paraffin-embedded tissue and stained with 0.1% methylene blue. The lesions were microdissected under a light microscope, and only areas with the pathological lesion were taken for DNA extraction. Apart from scanty amounts of contaminating inflammatory and stromal cells, we estimated that ≥70% of the resulting DNA was from the epithelial components of the serrated polyps. DNA was extracted using standard protocols. In total, 69 sporadic serrated polyps from 63 individuals generated adequate DNA of

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[3] The abbreviations used are: MEK, mitogen-activated protein/extracellular signal-regulated kinase kinase; MAP, mitogen-activated protein; ERK, extracellular signal-regulated kinase; HP, hyperplastic polyp; HP/AD, admixed hyperplastic polyp/adenoma; SA, serrated adenoma; MSI, microsatellite instability.

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quality suitable for *BRAF* and *KRAS* analysis. This study was approved by the Ethics Committee of the University of Hong Kong.

Mutation Screening of *BRAF* and *KRAS*. The complete coding sequences of exons 11 (G loop region) and 15 (activation segment) of *BRAF* and exon 2 of *KRAS* were amplified using intronic primers and directly sequenced on both strands using the DYEnamic ET Terminator Cycle Sequencing Kits (Amersham Pharmacia) and analyzed by the Applied Biosystems 377 or 3700 automated sequencer. These covered most of the mutation hot spots known previously of the two genes. All mutations were reconfirmed by independent PCR reactions and sequencing. The primers for *BRAF* sequencing of exon 15 were similar as described previously (3). The primers for exon 11 of *BRAF* (forward- TTC TGT TTG GCT TGA CTT GAC TT and reverse- ACT TGT CAC AAT GTC ACC ACA TT) and exon 2 of *KRAS* (forward- CTG AAA ATG ACT GAA TAT AAA CTT GT and reverse- ATA TGC ATA TTA AAA CAA GAT TTA CC) were designed to amplify a shorter fragment suitable for use in paraffin DNA. In each case with mutation, the percentage of mutant population was estimated by the quotient of mutant peak height over mutant plus wild-type peak height.

Analysis of MSI. Because corresponding normal tissue was not available, microsatellite analysis was performed using three monomorphic microsatellite markers, including BAT25, BAT26, and transforming growth factor βR II. The procedure was similar to those described in our previous publications (4, 32).

Statistical Analysis. Categorical variables were compared with the use of the χ^2 test with Yates correction or Fisher's exact test as appropriate.

RESULTS

Sixty-nine sporadic serrated polyps from 63 patients were suitable for the present study. These included 50 typical HPs, 10 HP/ADs, and 9 SAs. Thirty-nine polyps were from male patients, and 30 were from female patients. Twenty-two were from the right colon, and 46 were from the left colon (the tumor location in one case was not known). The 50 HPs showed no epithelial cell dysplasia. Of the 19 HP/ADs and SAs, 14 showed mild, 4 moderate, and 1 severe dysplasia. The size of these polyps ranged from 2 to 20 mm in maximal dimension (mean = 6.57 mm).

The incidence of *BRAF* and *KRAS* mutations and their relationship to clinicopathological features is shown in Table 1. Of the 69 serrated polyps studied, there were 29 cases (42%) with *BRAF* mutations and 15 cases (21.7%) with *KRAS* mutations. The spectra of *BRAF* and *KRAS* mutations found are shown in Table 2. Representative sequence chromatographs are shown in Fig. 1. Twenty-eight of the 29 *BRAF* mutations are in exon 15 with only one located within exon 11, and 26 involve codon 599 (25 V599E, 1 V599M), shown previously to be a mutation hot spot. The other *BRAF* mutations are G468A, D586E, and F594L. The V599M and D586E are novel mutations that have not been reported before. In 72% of cases with *BRAF* mutation, the mutant allele constitutes 35–66% of the total mutant and wild-type signal, suggesting that these are heterozygous mutations present in

Table 1 *Incidence of BRAS and KRAS mutations and their relationship to clinicopathological features of serrated polyps*

	Total	No. of *BRAF* mutation (%)	No. of *KRAS* mutation (%)	No. of *BRAF* or *KRAS* mutation (%)
Sex				
M	39	15 (39)	9 (23)	24 (62)
F	30	14 (47)	6 (20)	20 (67)
Tumor side				
Right	22	10 (46)	3 (14)	13 (59)
Left	46	19 (41)	12 (26)	31 (67)
Diagnosis				
HP	50	18 (36)	9 (18)	27 (54)
HP/AD	10	2 (20)	6 (60)[a]	8 (80)
SA	9	9 (100)[b]	0 (0)	9 (100)
Dysplasia				
Nil	50	18 (36)	9 (18)	27 (54)[c]
Mild	14	10 (71)	3 (21)	13 (93)
Moderate	4	1 (25)	2 (50)	3 (75)
Severe	1	0 (0)	1 (100)	1 (100)

[a] Fisher's exact test, HP/ADs *versus* HPs, $P = 0.009$; HP/ADs *versus* HPs + SAs, $P = 0.005$.
[b] Fisher's exact test, SAs *versus* HPs, $P < 0.001$; SAs *versus* HPs + HP/ADs, $P < 0.001$.
[c] χ^2 test with Yates correction, dysplasia Nil *versus* mild to severe, $P = 0.014$.

Table 2 *Mutation spectrum of BRAF and KRAS in 69 serrated polyps*

BRAF mutations[a]		HP $n = 50$	HP/AD $n = 10$	SA $n = 9$	Total $n = 69$
Nucleotide	a.a.				
T1796A	V(599)E	15	2	8	25
G1795A	V(599)M[b]			1	1
G1403C	G468A	1			1
C1758G	D586E[b]	1			1
T1782G	F594L	1			1
KRAS mutations					
Nucleotide	a.a.				
G35A	G12D	4	4		8
G35T	G12V	2			2
G35C	G12A	1	1		2
G34T	G12C	1			1
G38A	G13D	1	1		2

[a] *BRAF* and *KRAS* mutations are mutually exclusive, χ^2 with Yates correction, $P = 0.001$.
[b] Novel *BRAF* mutations.

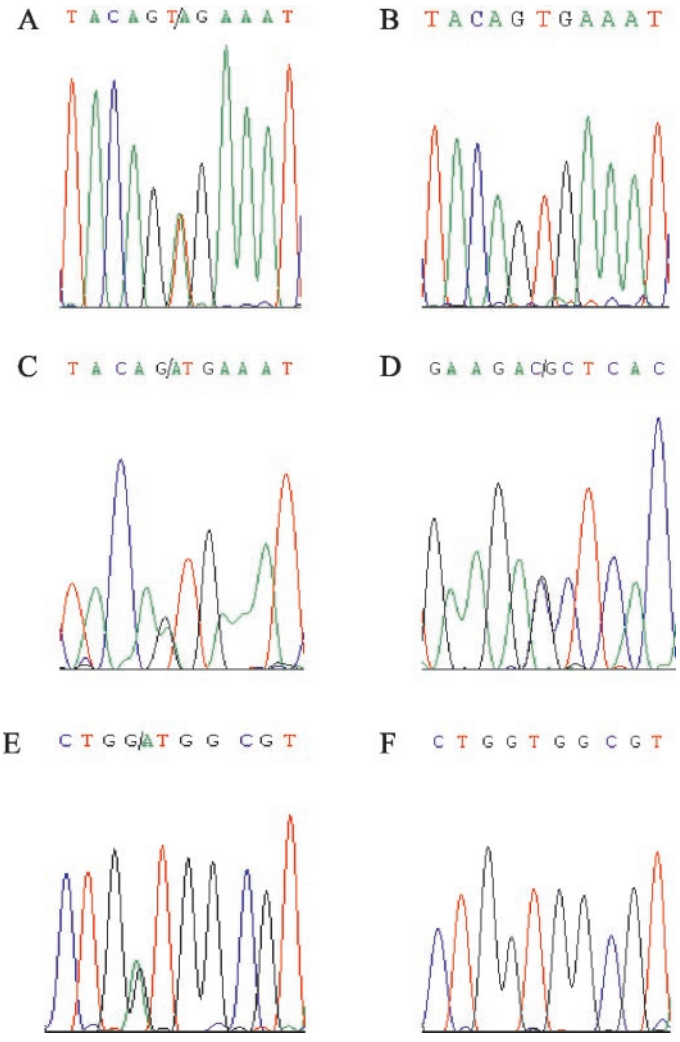

Fig. 1. Sequence chromatographs of serrated polyps with *BRAF* or *KRAS* mutations. *A*, a SA with V599E (T1796A) mutation of *BRAF*. *B*, an HP without *BRAF* mutation. *C*, an SA with V599M (G1795A) mutation of *BRAF*. *D*, an HP with D586E (C1758G) mutation of *BRAF*. *F*, an admixed HP/AD with G12D (G35A) mutation of *KRAS*. *G*, an HP with no *KRAS* mutation.

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most of the epithelial cells within the lesion. The remaining eight cases harbor mutant *BRAF* alleles that account for 20–32% of the total signal. The five cases with the lowest percentage of mutant alleles (20–24%) are all HPs. It is likely that these lower signals represent mutations present in a subpopulation of the lesion. For the 15 serrated polyps with *KRAS* mutations, the percentage of mutant alleles ranged from 20 to 71%. None of the polyps that carry a *BRAF* mutation have a *KRAS* mutation ($P = 0.001$, χ^2 with Yates correction).

Thirty-six percent (18 of 50) of HPs, 20% (2 of 10) of HP/ADs, and all (100%, 9 of 9) of SAs have *BRAF* mutations. Eighteen percent (9 of 50) of HPs, 60% (6 of 10) of HP/ADs, and none (0%, 0 of 9) of SAs have *KRAS* mutations. The associations of *BRAF* mutations with SAs (Fisher's exact test, SAs *versus* HPs, $P < 0.001$; SA *versus* HP+ HP/ADs, $P < 0.001$) and *KRAS* mutations with HP/ADs (Fisher's exact test, HP/AD *versus* HP, $P = 0.009$; HP/AD *versus* HP + SA, $P = 0.005$) are statistically significant. Overall, 64% of serrated polyps (44 of 69) harbor mutations in either *BRAF* or *KRAS*. Ninety percent (17 of 19) of the serrated polyps showing dysplasia had mutations (11 *BRAF* and 6 *KRAS*), significantly different from those without dysplasia (54%, 27 of 50; χ^2 test with *Yates* correction, $P = 0.014$). All 69 serrated polyps were microsatellite stable.

DISCUSSION

We have shown that *BRAF* mutations are present in 42% of serrated polyps. Similar to most other tumors, conversion of valine 599 to glutamic acid is the most common mutation found in serrated polyps (86% of mutations observed). This substitution results in the insertion of a negatively charged residue adjacent to a site of regulatory phosphorylation at T598 which may mimic normal regulatory phosphorylation and lead to constitutive activation of BRAF independent of RAS. *KRAS* and *BRAF* mutations appear to be mutually exclusive, confirming previous suggestions that they have similar biological consequences (3–5). The combined incidence of *BRAF* and *KRAS* mutations in serrated polyps is 64%, indicating that activation of the RAS-RAF-MEK-ERK-MAP kinase pathway constitutes a highly significant event in the pathogenesis of this group of lesions. The occurrence of either *BRAF* or *KRAS* mutations in 54% of otherwise histologically "innocuous" HPs suggests that these may be early steps in the initiation of the serrated neoplasia pathway. However, the presence of epithelial dysplasia is associated with even higher rates (90%) of mutation in either *BRAF* or *KRAS*, highlighting the importance of activation of the RAS-RAF-MEK-ERK-MAP kinase pathway in the progression of serrated neoplasms.

There is strong evidence in support of a pathway to colorectal carcinogenesis through serrated polyps: (*a*) morphological studies have reported evolution of HP to invasive carcinoma (sometimes through intermediate lesions of SA and HP/AD; Refs. 18–21) and have shown that 11% of SAs harbor foci of intramucosal cancer (17); and (*b*) patients affected by the rare hyperplastic polyposis have an increased risk of colorectal cancer (33–38), and some of these polyps in fact manifest the morphology of SAs (39).

The molecular basis of the serrated neoplasm–colorectal carcinoma sequence is currently poorly characterized. Previous studies have shown heterogeneity of genetic alterations in SAs, some suggesting a higher frequency of p53 mutation (25), loss of heterozygosity (22), MSI (23), and CpG island methylator phenotype (40, 41) in these lesions compared with HPs. However, the involvement of the RAS-RAF-MEK-ERK-MAP kinase pathway in the progression has been questioned. Despite the presence of *KRAS* mutations in 11–47% of HPs (22, 26, 29), in SAs, most studies have reported a low incidence (5–18%; Refs. 22, 30, and 42), raising the possibility of an alternative mechanism for early evolution. Our finding of *BRAF* mutations in all of the SAs examined, therefore, serves to provide a missing link in the pathogenesis of serrated neoplasms. The data suggest that acquisition of a *BRAF* mutation is associated with the progression of HP to SA, whereas progression to HP/AD is predominantly associated with acquisition of a *KRAS* mutation.

MSI has been reported previously in serrated polyps. It has therefore been proposed that serrated polyps may be the precursors of microsatellite unstable/mismatch repair-deficient colorectal cancers (23, 24, 43). Moreover, Rajagopalan *et al.* (5) have recently suggested that *BRAF* mutations are positively associated with MSI in colorectal cancer. These findings prompted us to examine MSI in our series of serrated polyps. Using three monomorphic microsatellite markers, we did not detect instability in any of the 69 serrated polyps studied. Taken together with our previous data (4), we do not observe a relationship between MSI and *BRAF* mutations in colorectal epithelial neoplasms. The lack of MSI in our series of serrated polyps is not surprising, given the fact that only three of our HP/ADs are located in the right colon, and the monomorphic microsatellite markers predominantly detect those with high level MSI. Even in previous studies, high level MSI is uncommon in serrated polyps, and most is restricted to HP/ADs occurring in the proximal colon (23, 41).

The relative contributions of the serrated neoplasm–carcinoma sequence compared with the classical AD-carcinoma pathway in colorectal cancer development have been difficult to assess. Morphological studies have been of limited utility because serrated lesions are usually small and can easily be destroyed by overgrowth of the cancers that subsequently develop. Nevertheless, by identifying remnant SA elements at the edge of invasive colorectal cancers, it has been estimated that ~6% of sporadic colorectal cancers originate from an SA (18). Molecular studies have also yielded few insights because there have been previously no known molecular changes that specifically characterize the serrated neoplasm–carcinoma pathway. The high frequency of *BRAF* mutations in HP (30%) and SA (100%) reported here is in sharp contrast to the low incidence observed in classical ADs (2.8%; Ref. 4). We therefore propose that the group of colorectal cancers carrying *BRAF* mutations (estimated at between 5 to 10%) may have evolved, at least in part, from HP through the intermediate stage of SA. However, the high incidence of *BRAF* mutations in HPs and particularly SAs compared with that observed in colorectal cancer suggests that the majority of colorectal cancers do not evolve through this pathway. HPs that progress through HP/ADs predominantly have *KRAS* mutations. This makes the adenomatous components of HP/ADs indistinguishable from classical ADs both at the morphological and molecular levels. Hence, their contribution to colorectal cancer is more difficult to assess.

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