World Journal of Gastroenterology

Online Submissions: http://www.wjgnet.com/esps/
bpgoffice@wjgnet.com
doi:10.3748/wjg.v20.i10.2634

World J Gastroenterol 2014 March 14; 20(10): 2634-2640
ISSN 1007-9327 (print) ISSN 2219-2840 (online)

Serrated pathway in colorectal carcinogenesis

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Received: May 3, 2013 Revised: June 15, 2013
Accepted: July 4, 2013
Published online: March 14, 2014

Abstract

Serrated adenocarcinoma is a recently described subset of colorectal cancer (CRC), which account for about 10% of all CRCs and follows an alternative pathway in which serrated polyps replace the traditional adenoma as the precursor lesion to CRC. Serrated polyps form a heterogeneous group of colorectal lesions that includes hyperplastic polyps (HPs), sessile serrated adenoma (SSA), traditional serrated adenoma (TSA) and mixed polyps. HPs are the most common serrated polyp followed by SSA and TSA. This distinct histogenesis is believed to have a major influence in prevention strategies, patient prognosis and therapeutic impact. Genetically, serrated polyps exhibited also a distinct pattern, with KRAS and BRAF having an important contribution to its development. Two other molecular changes that have been implicated in the serrated pathway include microsatellite instability and the CpG island methylator phenotype. In the present review we will address the current knowledge of serrated polyps, clinical pathological features and will update the most recent findings of its molecular pathways. The understanding of their biology and malignancy potential is imperative to implement a surveillance approach in order to prevent colorectal cancer development.

Key words: Serrated pathway; Colorectal carcinogenesis; Mutation; Microsatellite instability; CpG island methylator phenotype

Core tip: This paper reviews the pathologic and molecular features of serrated polyps and the serrated pathway to colorectal cancer and its clinical impact. The serrated pathway has recently emerged as the second pathway leading to colorectal cancer, and the genetic alterations occurring in this pathway are not still clarified. It's imperative to understand the molecular profile of colorectal lesions with higher malignancy potential to implement a surveillance and screening approach in order to prevent colorectal cancer development.

Yamane L, Scapulatempo-Neto C, Reis RM, Guimarães DP. Serrated pathway in colorectal carcinogenesis. *World J Gastroenterol* 2014; 20(10): 2634-2640 Available from: URL: http://www.wjgnet.com/1007-9327/full/v20/i10/2634.htm DOI: http://dx.doi.org/10.3748/wjg.v20.i10.2634

INTRODUCTION

Colorectal cancer (CRC) is the third most frequent cancer worldwide, with more than one million incident cases and is the fourth most common cause of cancer deaths accounting for approximately 609000 deaths[1]. In

Table 1 Frequency of hyperplastic polyps subtypes *n* (%)

Author	Population	HPs, *n*	MVHP	GCHP	MPHP
Kim *et al*[24]	South Korea	45	30 (66.7)	11 (24.4)	4 (8.9)
Carr *et al*[18]	Australia	36	34 (94.4)	2 (5.6)	0 (0.0)
Spring *et al*[27]	Australia	120	54 (45.0)	66 (55.0)	0 (0.0)

HP: Hyperplastic polyp; MVHP: Microvesicular hyperplastic polyp; GCHP: Globet cell hyperplastic polyp; MPHP: Mucin-poor hyperplastic polyp.

the classical genetic model for colorectal tumorigenesis described by Fearon and Vogelstein[2] the evolution of colorectal cancer follows the adenoma-adenocarcinoma sequence, which is driving by the progressive accumulation of a number of critical mutations[2]. In this model the adenomatous polyp is the principal precursor of colorectal cancer[2,3]. More than 90% of colorectal cancers are adenocarcinomas and subtypes include medullary, micropapillary, mucinous, serrated and signet ring cell[4]. Serrated carcinomas were first described by Jass and Smith[5] and represents the progression of a dysplastic serrated lesion, most commonly serrated adenomas. Serrated adenocarcinomas accounts for about 10% of all CRCs, and follows an alternative pathway in which serrated polyps replace the traditional adenoma as the precursor lesion to colorectal cancer[6]. Serrated polyps form an heterogeneous group of colorectal lesions that includes hyperplastic polyps (HPs), sessile serrated adenoma (SSA), traditional serrated adenoma (TSA) and a combination of two or more characteristics, formerly classified as mixed polyps (MP)[4,7-9]. This distinct histogenesis is also believed to have a major influence in prevention strategies, patient prognosis and therapeutic impact[6,10-12].

Molecularly, the classical adenoma-carcinoma sequence pathway is mainly governed by chromosomal instability (CIN) and *KRAS* mutations[3], whereas in the serrated pathway the genetic alterations include *BRAF* mutation and gene promoter hypermethylation (CpG island methylator phenotype or CIMP)[13]. Microsatellite instability (MSI) is another molecular pathway that can be detected in both the adenoma-carcinoma sequence and the serrated pathway[14,15].

Morphologically colorectal carcinomas that harbors CIN and arises from adenoma have a classical histological feature of dirty necrosis[6]. The carcinomas with microssatelite instability generally occurs in the right colon, are mucinous or poorly differentiated (medullary histology) and also have intraepithelial lymphocytes and lymphoid aggregates "Crohn like"[4]. The serrated carcinomas that originate from traditional serrated adenomas generally are MSS or MSI-L and those that originate from a sessile serrated adenoma are MSI-H. Some histological features are typically found and used to classify colorectal carcinoma as serrated carcinoma. The most important histological features are: presence of epithelial serrations, clear or eosinophilic cytoplasm, abundant cytoplasm, vesicular nuclei, absence of necrosis, mucin production and presence of cell balls and rods. Other very important histological finding that helps to make a diagnostic of serrated carcinoma is the presence of serrated lesion in the periphery of the infiltrative carcinoma[6].

Due to this well recognized step-wise progression of premalignant lesions to carcinomas, CRC has a particular and outstanding feature in that make it amenable to prevention strategies with detection of removal of those susceptible lesions[16]. Therefore, it is imperative to understand the lesions with higher malignancy potential and with the use of their molecular profile to implement a surveillance approach in order to prevent colorectal cancer development[17].

In this article, we review the pathologic and molecular features of serrated polyps and the serrated pathway to colorectal adenocarcinoma.

Morphological aspects of serrated polyps

The serrated polyps are characterized by the serrated morphology, hypermaturation of the gland epithelium due to low extent of the cell loss by apoptosis[18,19]. The classification of the serrated lesions by a pathologist is based mainly on architectural criteria like growth pattern, cytological dysplasia and serration of the crypts[4,8,19-21] (Figure 1). The reliable classification of serrated polyps is fundamental to surveillance of patients with these precursor lesions[4]. Yet, this is difficult task, due to the problems with accurate histological definition, leading to a high inter-observer variation, even among expert pathologists[4,8,13,19,21,22].

HPs are the most common serrated polyp of the colon accounting for about 80% to 90% of all serrated polyps and around 10% to 15% of all polyps of the colon. HPs are generally small (< 5 mm) and frequently located in the distal colon (75%-80% in the rectosigmoid)[6,23]. According to the World Health Organization, three subtypes of HP have been recognized: the microvesicular (MVHP), goblet-cell rich hyperplastic polyps (GCHP) and mucin-poor types (MPHP). The differences between them are based mainly in morphology and on the cellular mucin distribution[4,13,24]. All HPs subgroups are histopathology distinguished by elongation of the crypts with different degrees of serration[4,25] and tend to have no dysplasia[8]. MVHP, the most frequent subtype, is characterized by epithelial cells with vesicular mucin and decrease in the goblet cells, concomitantly with conspicuous serration often located in the basal portion of the crypts[4,13,24]. On the other hand, the GCHP has many mature cells in the upper crypt with subtle serration[4,13,26]. The MVHP is often seen in the right colon, whereas the GCHP is more frequently observed in the left-sided colon. The MPHP is rare and therefore, less frequently discussed. It seems to be more frequent in the left colon[6]. There are still great divergences about the frequency of each HP subtypes (Table 1). Spring *et al*[27] reported that MVHP was observed in 45% and GCHP in 55% of 120 hyperplastic polyps in the unselected series of 190 patients and 414 lesions. Recently, Kim *et al*[24] related that MVHP, GCHP and MPHP accounted with 66.7%;

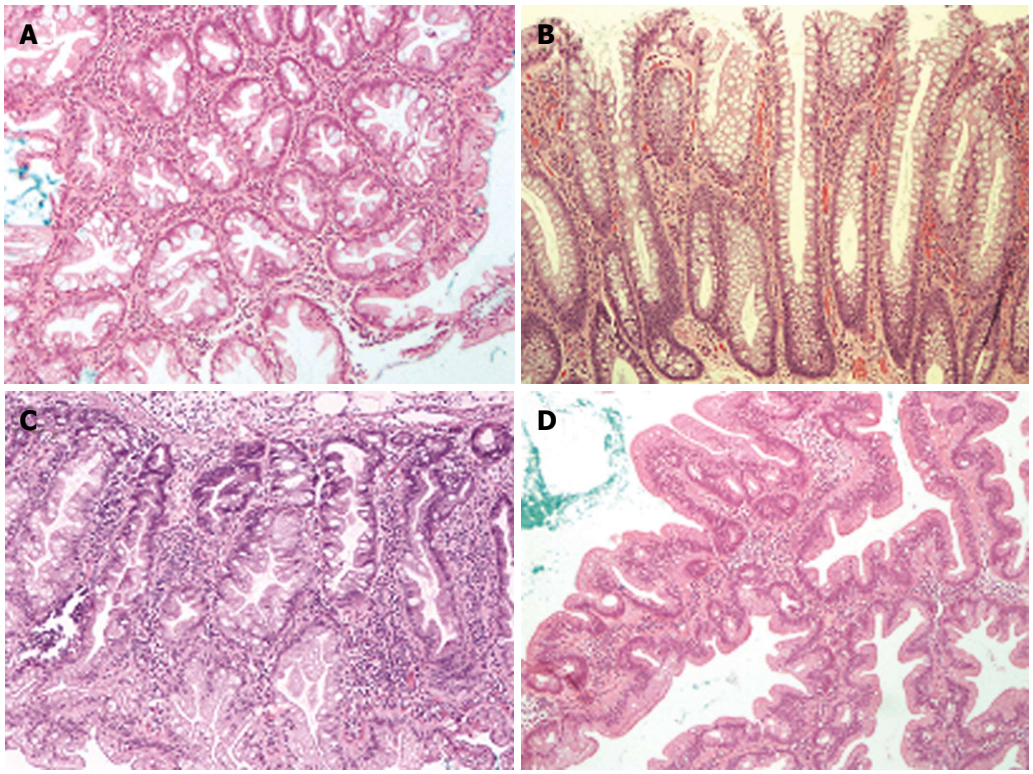

Figure 1 Hematoxylin and eosin of representative cases of serrated lesions. A: Microvesicular hyperplastic polyp (× 100); B: Goblet cell hyperplastic polyp (× 100); C: Sessile serrated adenomas (× 100); D: Traditional serrated adenomas (× 100).

24.4% and 8.9%, respectively, of the 45 HPs studied. On the other hand, Carr *et al*[18] found only 2 (5.6%) GCHPs among 34 HPs studied. Despite these divergences, the clinical relevance in the recognition of the HPs subtypes is still indefinite, suggesting that more studies are needed to clarify this aspect[13,25].

The SSAs account for about 3%-9% of all the colorectal polyps[18,21,27] and 10%-25% of all serrated polyps[4,26,27] and are generally located in the right colon. The TSAs are infrequent lesions, located predominantly in the left colon and account for about 1%-2% of the serrated lesions[18,27]. The histopathology characteristics of the SSA includes dilatation of the base of the crypts which often grow parallel to the muscularis mucosa forming L shaped or inverted T-shaped crypts (*anchor form*)[4,13,19]. SSAs have elongation of crypts with prominent serration[4,7,27]. These lesions might have subtle nuclear atypia, where mitoses may be seen in the crypts. Since the SSA has similarities with MVHP the classification is made based mainly in the analysis of the crypts: if two or three adjacent crypts demonstrate features of SSA, it must be classified into SSA[4]. When conventional cytological dysplasia is observed, the serrated polyps are classified as TSA[18]. Nonetheless, due to the similarities with conventional adenomas, it is recommended that this term never be used without qualifier[4]. The TSA has overall complex and villiform growth pattern, showing cells with cytological dysplasia that may indicates progression to carcinoma. TSA differ from SSA mainly because TSA lose the anchoring leading the formation of ectopic crypts[4,18]. Further, it is rare to observe mitosis in TSA and columnar cells with eosinophilic cytoplasm are features of these lesions[4,13].

MPs account for about 0.7%-1.5% of all colonic polyps and for 1.7% to 4.7% of the serrated polyps[18,27,28]. Mixed polyps combine at least two characteristics of conventional adenomas, SSA, TSA or HPs[18,21,28-30]. The main feature of MP is the combination of nondysplastic polyps (HP or SSA) with the dysplastic one (TSA or conventional adenomas)[21,27].

Serrated polyps and natural history of CRC: evidence linking serrated polyps with CRC

In the classic adenoma-carcinoma sequence model of colorectal tumorigenesis proposed by Fearon and Vogelstein, HPs were described as harmless non neoplastic lesions with no malignant potential[2,24,31]. Though, a new understanding of the pathology and natural history of CRC has emerged over the past decade. Approximately, 10% of sporadic colorectal cancers, named "serrated adenocarcinoma" will arise *via* serrated polyp-carcinoma sequence[11]. In this context, hyperplastic polyps were recently recognized as neoplastic lesions included in the serrated group and may predispose to cancer. In this new model, HPs may progress to other serrated polyp including sessile serrated adenomas, traditional serrated adenomas or mixed polyps and then evolve to colorectal cancer[32]. It has been estimated that HPs take 7.5 years to progress to serrated adenoma[33]. However, only a tiny percentage of hyperplastic polyps will progress to cancer[30,31,34,35]. Large and often right-sided HPs are more

Table 2 Description of molecular alterations reported in serrated lesions

Ref.	Population	Molecular alterations	Serrated polyp						Carcinoma
			HP			SSA	TSA	MP	Serrated ADC
			MVHP	GCHP	MPHP				
Kim *et al*[24]	South Korea	*KRAS*	16.7%	72.7%	25.0%	12.5%	NA	NA	NA
		BRAF	66.7%	0.0%	25.0%	60.7%	NA	NA	NA
		MSI-H	NA	NA	NA	1.8%	NA	NA	NA
		CIMP positive	73.3%	18.2%	75.0%	76.8%	NA	NA	NA
Sandmeier *et al*[30]	Switzerland	*KRAS*		17.0%		25.0%	NA	NA	NA
		BRAF		83.0%		63.0%	NA	NA	NA
		MSI-H		0.0%		0.0%	NA	NA	NA
		CIMP positive		NA		NA	NA	NA	NA
Kim *et al*[10]	United States	*KRAS*	6.0%	8.0%	NA	8.0%	17.0%	25.0%	NA
		BRAF	88.0%	75.0%	NA	81.0%	76.0%	75.0%	NA
		MSI-H	0.0%	0.0%	NA	0.0%	3.0%	0.0%	NA
		CIMP positive	41.%%	8.0%	NA	44.0%	43.0%	50.0%	NA
O´Brien *et al*[40]	United States	*KRAS*	13.2%	42.9%	NA	6.9%	NA	NA	0.0%
		BRAF	76.3%	21.4%	NA	82.9%	NA	NA	82.0%
		MSI-H	0.0%	0.0%	NA	0.0%	NA	NA	81.8%
		CIMP positive	47.4%	14.3%	NA	75.9%	NA	NA	90.0%
Spring *et al*[27]	Australia	*KRAS*	11.0%	50.0%	NA	8.0%	0.0%	43.0%	NA
		BRAF	70.0%	20.0%	NA	78.0%	66.0%	57.0%	NA
		MSI-H	NA	NA	NA	NA	NA	NA	NA
		CIMP positive	NA	NA	NA	NA	NA	NA	NA
Konishi *et al*[34]	Japan	*KRAS*		13.0%		8.0%	NA	22.7%	NA
		BRAF		NA		32.0%	NA	40.9%	NA
		MSI-H		8.0%		36.0%	NA	5.0%	NA
		CIMP positive		NA		NA	NA	NA	NA
Yang *et al*[33]	United States	*KRAS*	13.2%	46.2%	NA	7.1%	28.0%	NA	NA
		BRAF	76.3%	23.1%	NA	82.1%	60.0%	NA	NA
		MSI-H	NA	NA	NA	NA	NA	NA	NA
		CIMP positive	47.4%	15.4%	NA	75.0%	80.0%	NA	NA

HP: Hyperplastic polyps; MVHP: Microvesicular hyperplastic polyp; GCHP: Globet cell hyperplastic polyp; MPHP: Mucin-poor hyperplastic polyp; SSA: Sessile serrated adenoma; TSA: Traditional serrated adenoma; MP: Mixed polyp; MSI-H: High microsatellite instability; CIMP: CpG island methylator phenotype; ADC: Adenocarcinoma; NA: Not applicable.

likely to have malignant potential[35-37].

At the genetic level, there are also evidences showing that serrated polyps are strongly associated with the development of colorectal neoplasms, as further discussed.

Putative genetic pathways in serrated carcinomas

Serrated pathway has recently emerged as the second pathway leading to colorectal cancer, therefore, the genetic alterations occurring in this pathway are not clarified and there is great variability in the frequency of molecular changes described. Results of recent studies reporting genetic analysis in the serrated lesions are summarized in Table 2. A schematic view of serrated polyps-carcinoma sequence is shown in Figure 2.

The most frequent genetic alterations involve *BRAF* and *KRAS* mutations. Both *KRAS* and *BRAF* encodes kinases that belong to the mitogen-activated protein kinase (MAPK) cascade that mediates the cellular signaling involving cell proliferation, apoptosis and differentiation[38]. Mutations in *KRAS* and *BRAF* oncogenes result in the constitutive activation of the MAPK pathway and in uncontrolled cell proliferation, cell survival, invasion and metastisation[38]. Mutations in both oncogenes are frequently found as mutually exclusive events in serrated adenocarcinoma[39] and in the precursor serrated lesions[33]. Stefanius *et al*[39] demonstrated a high frequency of *KRAS* mutations (45.2%) in serrated adenocarcinoma, suggesting that a significant proportion of *KRAS* mutated CRC originates from serrated polyps. O´Brien *et al*[40] showed high frequency of *BRAF* mutation (V600E) among serrated carcinomas (82%), emphasizing that this mutation is a specific marker in the serrated pathway.

KRAS mutations occur predominantly at codon 12 and less frequently at codon 13, and the most common mutations are G12D, G12V and G13D[27], being mutated in 0%-73% of serrated polyps[6,10,27,30,33,34,40], 6%-73% of HPs, 7%-25% of SSA[10,24,27,30,33,34,40], and in 0%-28% of TSA[10,27] (Table 2). These codons are also the most frequent mutated in colorectal cancer[41]. Concerning *BRAF*, the most frequent mutation is V600E which occur in 0%-88% of HPs, 32%-82.9% of SSA, and in 60%-76% of TSA[24,27,33,34,40,42] (Table 2). *BRAF* mutations are more frequent than *KRAS* mutations in MVHP and SSA (Table 2)[24,27,33,34,40]. On the other hand, in GCHP, *KRAS* mutations are likely the most important genetic alteration. One study, by Kim *et al*[10] showed higher frequencies of *BRAF* mutations than *KRAS* mutation in both MVHP and GCHP.

Another molecular alteration described in serrated lesions is MSI, a hallmark of colorectal cancer arising

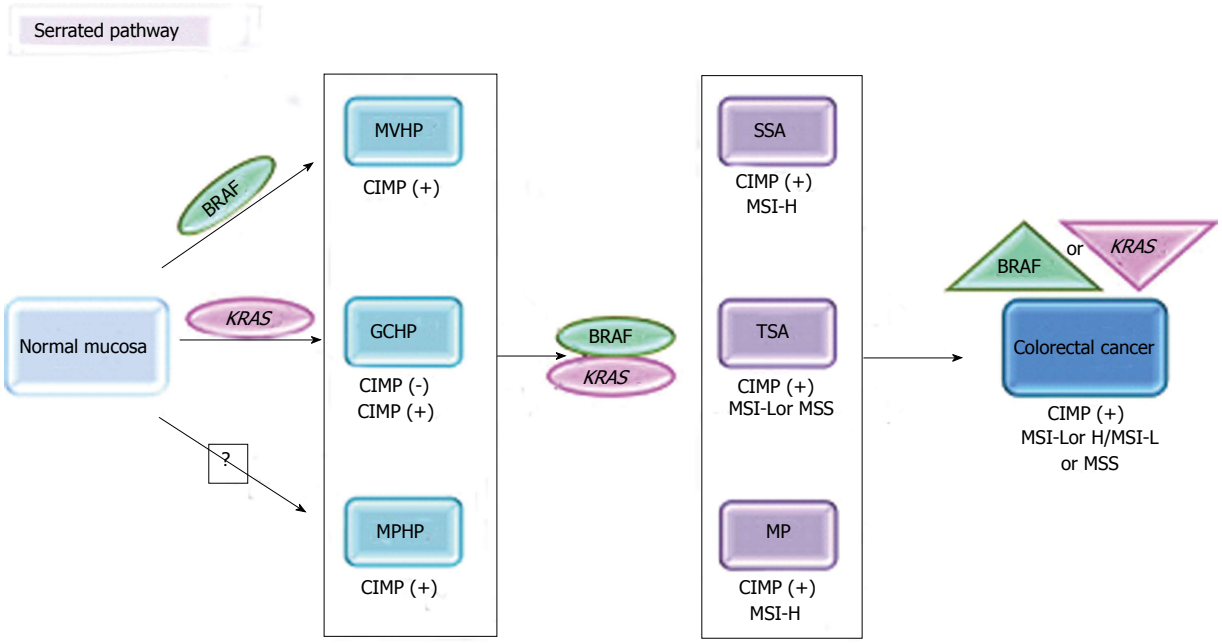

Figure 2 Schematic view of serrated polyps: Carcinoma sequence. MVHP: Microvesicular hyperplastic polyp; GCHP: Globet cell hyperplastic polyp; MPHP: Mucin-poor hyperplastic polyp; SSA: Sessile serrated adenoma; TSA: Traditional serrated adenoma; MP: Mixed polyp; MSI-H: High microsatellite instability; CIMP: CpG island methylator phenotype.

in the context of Hereditary Non Polyposis Colorectal Cancer or Lynch syndrome[43] (Table 2 and Figure 2). The MSI is caused by the lost of mismatch-repair genes[43], which leads to an increased susceptibility to accumulate mutations in genes with microsatellite regions[43]. The MSI status can be classified according to the markers that show instability[34]. It was proposed a panel of five microsatellites sequencing, known as Bethesda panel, for identify the MSI status[4,10,11,44]. This panel include two mononucleotide markers (BAT 25 and BAT 26) and three dinucleotide microsatellites (D5S346, D2S123 and D17S250), but three other mononucleotide markers can be included (NR21, NR22 and NR24) in a pentaplex PCR[45]. Tumors that have two or more unstable markers are considered high MSI (MSI-H), when only one marker is unstable tumors are defined as low MSI (MSI-L)[4,10,11,44], and tumors are defined as microsatellite stable (MSS), when no instability is identified at those five loci[4,11,44]. About 15%-20% of sporadic colorectal cancers are MSI-H. Importantly, MSI-H tumors exhibited a distinct genetic pathway of the MSS and MSI-L tumors, without major chromosomal alterations, but showed the presence of mutations in genes with microsatellite regions, known as MSI-target genes[4,24,44]. Stefanius *et al*[39] reported that 20.6% of serrated cancer showed MSI-H. Studies show that the precursor serrated lesions rarely demonstrate high levels of MSI (Table 2). Kim *et al*[10], observed that MSI-H was presented in 3.0% of TSA (Kim, 2008). Contrastingly, Konishi *et al*[34] reported that MSI-H was observed in 36% of sessile serrated adenomas (Table 2).

The CpG island methylator (CIMP) phenotype is also strongly related to the colorectal serrated carcinogenesis[24,44] (Table 2 and Figure 2). The methylation in the CpG island may cause transcriptional silencing, and inhibits gene expression by the binding of methyl groups to recurrent cytosine-guanine dinucleotides sequences, commonly in promoter region. This is an epigenetic event observed in the precursor serrated lesions and colorectal polyps[4,10]. The CIMP is frequent in serrated polyps mainly in the proximal colon[13]. The phenotype of CpG island methylator in hyperplastic polyps account for 41.0%-73.3% of MVHP, 8.0%-18.2% of GCHP and 75% of MPHP[24,33] (Table 2). Among serrated adenomas, CIMP-H is frequently observed in 44.0%-76.8% of SSA[24,33,40] and in 43%-80% of TSA[10]. Aberrant hypermethylation of CpG island is more frequently associated with *BRAF* mutation than with *KRAS* mutation in serrated cancers. It is frequently described that serrated lesions with *KRAS* mutation demonstrate low levels of CIMP distinctly to *BRAF* serrated lesions, often characterized by CIMP-H (Figure 2 and Table 2). High frequency of methylation was associated with polyps with large size that are > 1 cm and with high-grade dysplasia[10]. The status of CIMP is also often correlated with MSI status and mutations in both, *KRAS* and *BRAF* oncogenes[3,4,8,29]. According to Sandmeier *et al*[30], *BRAF* mutations were associated with *MLH1* and/or *p16* methylation in 88% of right-sided SSAs.

Clinical impact of the serrated pathway

Understanding of natural history and malignant potential of colorectal polyps is essential for management of these lesions. After complete removal of adenomatous polyps, surveillance recommendations are well established based on risk for subsequent adenomas[14]. On the other hand, there is still lack of studies of follow up intervals of ser-

rated polyps and more accurate information about management of serrated polyps of the colon is not yet available[17,23]. The great majority of serrated polyps will never progress to carcinoma, nevertheless, it has been described that some patients harboring mainly sessile serrated lesions larger than 10 mm have increased risk to develop neoplasia. Therefore, despite absence of controlled studies TSA and SSA have been included among the lesions requiring surveillance[23]. Detecting and removing theses lesions may contribute to the prevention of colorectal cancer arising *via* the serrated pathway.

In addition, there is also growing evidence that cancers arising through the serrated pathway may differ from cancers arising through adenoma pathway in their prognosis and response to therapy. Serrated adenocarcinoma is likely to have a less favorable 5-year survival than conventional cancers[6,12]. The differences in the MSI status in the serrated adenocarcinomas may have therapeutic implications, which require that the patient be followed carefully[6,46,47].

The knowledge of serrated pathway during colorectal carcinogenesis represents a clinical challenge in the surveillance of patients harboring serrated polyps. Despite of gaps in our knowledge about biological behavior of serrated polyps, the molecular alterations reported so far, has allowed the understanding of serrated carcinogenesis and paving the way for future direction in CRC prevention.

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ISSN 1007-9327