The serrated polyp pathway to colorectal carcinoma

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Abstract

The serrated polyp pathway comprises a morphologically distinct group of colorectal neoplasms and represents an alternative molecular pathway to colorectal cancer. The earliest lesion is a non-dysplastic serrated polyp (hyperplastic polyp) or precursor serrated aberrant crypt focus with an activating mutation of the *BRAF* oncogene; this may progress via an atypical hyperplastic polyp variant (sessile serrated adenoma) to a dysplastic serrated polyp (serrated adenoma) and ultimately to a carcinoma that exhibits distinctive histological and molecular genetic characteristics. The progress of non-dysplastic serrated polyps to more advanced neoplasms is associated with increasing levels of CpG island methylation, leading to inactivation of key mutator and tumour-suppressor genes. The carcinomas of this pathway frequently exhibit microsatellite instability due to epigenetic silencing of hMLH1. A second, less well-defined arm of this pathway is associated with *KRAS* mutations, low levels of CpG island methylation and endpoint microsatellite-stable carcinomas that exhibit chromosomal instability and histological features similar to those of *APC*-mutated carcinomas of the conventional adenoma–carcinoma sequence.

Keywords *BRAF*; CIMP; dysplasia; hyperplastic polyp; *KRAS*; microsatellite instability; serrated adenoma; serrated carcinoma; serrated polyp; sessile serrated adenoma

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Basic concepts

Serration, an apt histological term for a saw-toothed glandular architecture, has been linked primarily to the common diminutive mucosal growths of the colorectum, called hyperplastic or metaplastic polyps. Although contrarian views can be found in the literature,[1,2] the conventional wisdom, since their early description and distinction from adenomatous polyps,[3] has been that such serrated polyps are self-limited and unrelated to colorectal carcinoma (CRC). That view has been altered over the past decade, principally by advances in our knowledge of the molecular genetics of sporadic CRC with microsatellite instability (MSI)[4] and the clinicopathological[5] and molecular delineation of the syndrome of hyperplastic polyposis.[6] Serrated polyps are now understood to encompass an array of colorectal polyps, collectively referred to as the 'serrated polyp pathway', that play a major role in the histogenesis of upwards of 15% of CRCs.[7] Applied to the projected incidence of CRC in the USA for 2007,[8] this statistic yields an estimate of 23,000 new cases of serrated polyp pathway cancers, greater by 50% than the expected incidence of oesophageal cancer and by 10% that of gastric cancer (Figure 1).

The serrated polyp pathway (Figure 2) describes a morphological sequence that originates in a hyperplastic polyp or a precursor aberrant crypt focus (ACF),[9] and progresses via an atypical hyperplastic polyp variant to a serrated polyp with overt dysplasia, and ultimately to serrated carcinoma. In addition to a morphological appearance that differs from the polyps of the conventional adenoma–carcinoma sequence, at the molecular level this group of colorectal neoplasms also represents an alternative molecular pathway to colorectal cancer, as originally suggested by Jass *et al.*[4] The predominant instigating mutation of this pathway is an activating mutation of the oncogene *BRAF*, and the predominant endpoint carcinomas show defective DNA mismatch repair, resulting in microsatellite instability (MSI-high); but they also include some proportion of carcinomas that are microsatellite stable (MSS) or MSI-low.[10] The alternative that this pathway represents is to the more frequent or 'garden variety' CRC of the adenoma–carcinoma sequence distinguished by instigating adenomatous polyposis coli (*APC*) gene mutations and endpoint carcinomas that are characterized by chromosomal instability.[4,11,12]

Non-dysplastic serrated polyps (hyperplastic polyps)

The terms 'hyperplastic polyp' or 'metaplastic polyp' are widely used in pathology, but current knowledge justifies a classification of these non-dysplastic serrated polyps that recognizes their heterogeneity, and which identifies those categories that have a measurable level of risk of progression or association with malignant transformation. Efforts in this direction have made progress, but some confusion exists and a consensus on terminology and criteria is awaited. The classification of serrated polyps in this review draws on the literature and attempts, using existing terms, to group histologically well-defined categories according to their molecular genetic profiles and the current knowledge of their biology and clinical behaviour. Torlakovic and Snover[5] first drew attention to an atypical hyperplastic polyp variant in a study of a small series of patients with hyperplastic polyposis. It was distinguished by larger size and more proximal location than

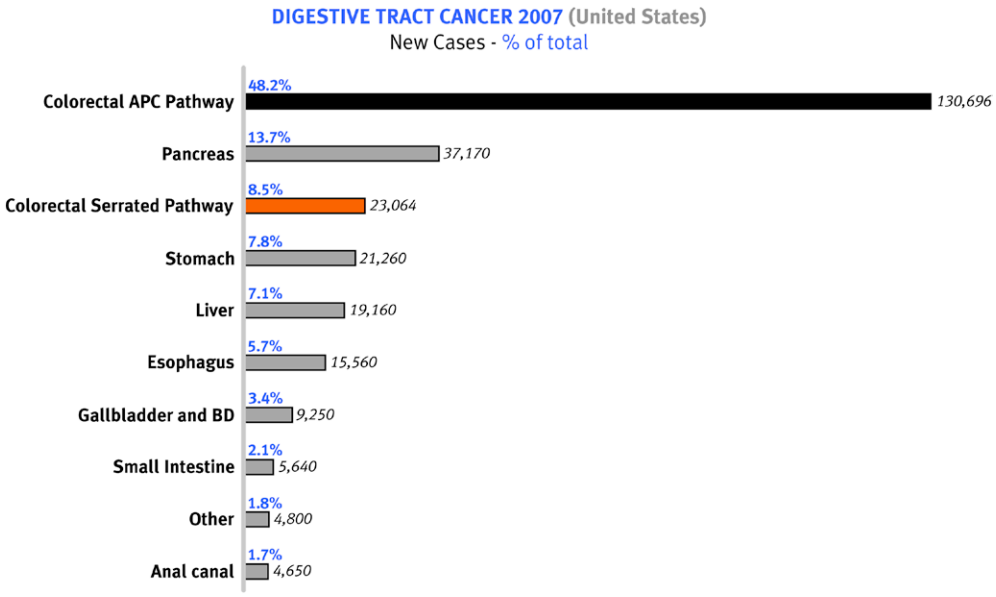

Figure 1 Contribution of serrated carcinoma to the cancer burden of the digestive tract. Bar graph of the projected incidence of digestive disease cancers in the USA for 2007 by organ site, based on statistics from the American Cancer Society.[8] Colorectal cancer is presented as *APC* pathway and serrated pathway groups, assuming that the latter group represents 15% of the total incidence of colorectal cancer (see text). Bars correspond to numbers for each category and to the percentage (blue font) of the total number of incident digestive tract cancers.

a typical hyperplastic polyp, and histologically by architectural distortion of the crypts and variable degrees of cytological atypia. They postulated that this hyperplastic polyp was:

- more akin to a serrated adenoma as described by Longacre and Fenoglio–Preiser[13]
- neoplastic rather than hyperplastic
- a likely precursor of carcinoma in patients with this syndrome.

They proposed the term 'sessile serrated adenoma' because these polyps were frequently sessile.

Informed by these observations, and because of later progress in molecular genetics that linked serrated polyps with sporadic MSI CRC,[4] Torlakovic *et al.*[14] subsequently evaluated the histological spectrum of sporadically occurring hyperplastic polyps by applying a panel of 24 different histological parameters to 289 hyperplastic polyps. A cluster analysis statistical methodology showed that these several thousand data points could be segregated into three major groups or histological subtypes:

- serrated polyp with microvesicular mucin (MVSP)
- goblet cell serrated polyp (GCSP)
- sessile serrated adenoma (SSA; Figures 3 and 4).

A fourth uncommon and less well-defined variant, mucin-depleted, was also described.

Since that report, molecular genetic studies have shown associations between serrated polyps and coherent molecular genetic and clinicopathological profiles.[10,15–20] Such studies have also provided evidence that hyperplastic polyps represent clonal proliferations of genetically altered epithelial cells of the colorectal mucosa and are thus *de facto* neoplasms. As such, all variants might, by strict taxonomic rule, be entitled to the label 'adenoma', but the convention that adenoma in the colon is applied

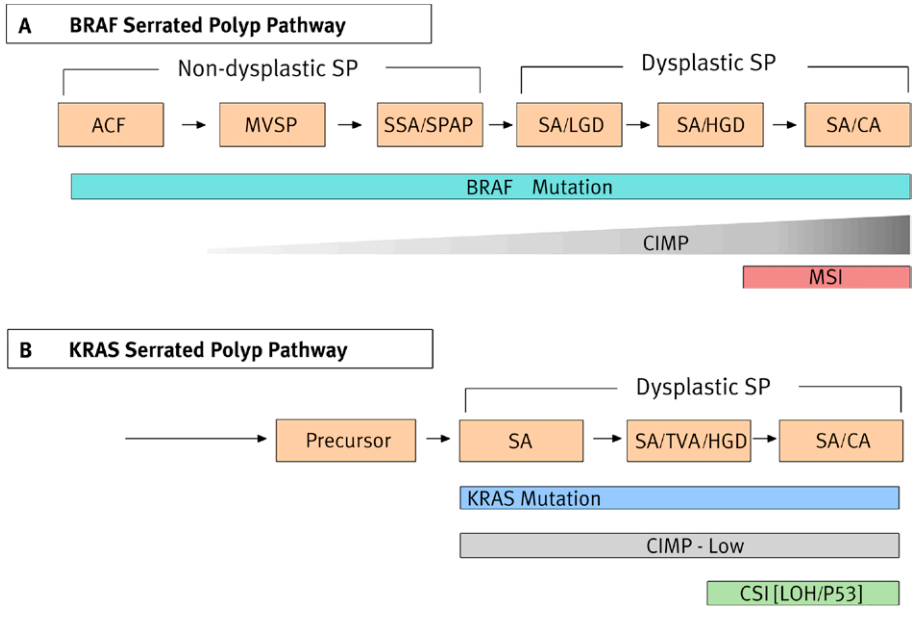

Figure 2 A *BRAF*-mutated serrated polyp pathway. The diagram depicts $BRAF^{V600E}$ as an early or instigating mutation originating in a serrated aberrant crypt focus (ACF); CpG-island methylation is increasing with advancing histological stage, and MSI-high is occurring late, at the interface of serrated adenoma, high-grade dysplasia (HGD) and invasive carcinoma (SA/CA). **B** *KRAS*-mutated serrated polyp pathway. *KRAS*-mutated serrated adenoma progresses to a mixed tubulovillous adenomatous phenotype (TVA) and acquires high-grade dysplasia (HGD). The progression is contributed to by CIMP-low, followed later by the development of chromosomal instability and LOH of key suppressor genes. The interface of high-grade dysplasia (HGD) and infiltrating carcinoma (SA/CA) is associated with p53 mutation. (Elsevier copyright in: O'Brien MJ. Hyperplastic and serrated polyps of the colorectum. *Gastroenterol Clin North Am* 2007; **36:** 947–968).