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REVIEW

Colorectal serrated adenocarcinoma

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Colorectal cancer (CRC) ranks among the three most common cancers in terms of both cancer incidence and cancer-related deaths in most Western countries. Serrated adenocarcinoma is a recently described, distinct variant of CRC, accounting for about 7.5% of all CRCs and up to 17.5% of most proximal CRCs. It has been postulated that about 10–15% of sporadic CRCs would have their origin in serrated polyps that harbour a significant malignant potential. These lesions include hyperplastic-type aberrant crypt foci, hyperplastic polyps, sessile serrated adenomas, admixed polyps and serrated adenomas, and constitute the so-called 'serrated pathway', which is distinct from both the conventional adenoma–carcinoma pathway and the mutator pathway of hereditary non-polyposis CRC and is characterized by early involvement of oncogenic *BRAF* mutations, excess CpG island methylation (CIM) and subsequent low- or high-level DNA microsatellite instability (MSI). Methylation of *hMLH1* is likely to explain the increased frequency of high-level MSI (16%) and methylation of *MGMT* is postulated to explain the low-level MSI (29%) in serrated adenocarcinomas. Reproducible histopathological criteria for serrated adenocarcinoma have recently been established and they have been qualified by DNA expression analysis for 7928 genes, showing clustering of serrated adenocarcinomas into a molecular entity apart from conventional adenocarcinoma, and representing with distinct down-regulation of *EPHB2*, *PTCH* and up-regulation of *HIF1α*.

Keywords: colonic polyps, colorectal neoplasms, intestine, large, serrated adenocarcinoma, serrated adenoma

Abbreviations: ACF, aberrant crypt foci; ACF-D, dysplastic type of aberrant crypt foci; ACF-H, hyperplastic/heteroplastic type of aberrant crypt foci; BM, basement membrane; BMI, body mass index; CIMP, CpG island methylator phenotype; CRC, colorectal cancer; FAP, familial adenomatous polyposis; HIF, hypoxia-inducible transcription factors; HNPCC, hereditary non-polyposis colorectal cancer; LOH, loss of heterozygosity; MAPK–ERK, mitogen-activated protein kinase–extracellular signal-regulated kinase; MGMT, O6-methylguanine-DNA methyltransferase; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, high-level microsatellite instability; MSI-L, low-level microsatellite instability; MSS, microsatellite stable

Introduction

Colorectal cancer (CRC) is one of the three most common cancers, with an estimated worldwide incidence of more than 570 000 new cases per year. Lifetime risk of CRC may reach 6% of the population in industrialized countries.[1,2] For an individual patient, the risk of CRC would be significantly reduced if all precursor lesions were removed by endoscopical polypectomy. This has been observed in many surveillance studies, reflected in the guidelines for CRC screening, colonoscopy surveillance and treatment of patients with adenomas.[3–6] However, these large cohort studies have also shown that a significant number of CRCs will still develop despite close surveillance.[3,4] Such interval cancers may have been missed in a previous endoscopy, or they may be a result of either rapid cancer development[4,7] or inappropriate recognition of their

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precursor lesions in endoscopy. All these possibilities could be explained by a lack of recognition of lesions we now call serrated adenomas and sessile serrated adenomas.[8–14] The serrated pathway represents an alternative pathway to CRC,[15–24] which may explain at least 7.5% of all and up to 17.5% of proximal CRCs. The histomorphological characteristics predicting the severity of the cancer risk of these polyps are not yet well determined and it is important to know which lesions and markers predict a significant cancer risk in serrated polyps. This review attempts to relate colorectal serrated adenocarcinoma to its precursor lesions and discusses the potential genetic and epigenetic mechanisms that have been associated with the serrated neoplasia pathway.

Morphology of serrated pathway lesions

The term 'serrated polyp' is used for a range of colorectal polyps, from ordinary hyperplastic polyps to serrated adenoma, with sawtooth-like infolding of the surface and crypt epithelium in common. Serrated infolding of the epithelium has been considered to be the result of decreased apoptosis and delayed migration of the cells from crypt to surface.[25,26] Putative precursor lesions for all serrated polyps are the hyperplastic/heteroplastic subtype of aberrant crypt foci (ACF).[27–29] The currently proposed classification divides serrated polyps into four morphological categories (hyperplastic polyps, sessile serrated adenomas, admixed polyps and traditional serrated adenomas, Table 1)[11,13] which have not yet been ranked exactly according to their pathobiological relationships.

Table 1. Classification of serrated lesions

Aberrant crypt foci (heteroplastic/hyperplastic)
Sessile serrated lesions
Sessile serrated adenoma
Admixed polyp (sessile serrated adenoma with dysplastic area)
Serrated adenocarcinoma
Polypoid serrated lesions
Hyperplastic polyp
Microvesicular
Goblet cell
Mucin poor
Serrated adenoma
Serrated adenocarcinoma

ABERRANT CRYPT FOCI

The earliest lesions attributed to participate in the serrated pathway are ACF.[29–33] They were first observed in animal experiments, where the earliest possible alterations induced by known intestinal carcinogens were sought[34] and thereafter in humans in association with CRC in resection specimens.[35,36] There are two types of ACF, hyperplastic/heteroplastic type (ACF-H) and dysplastic type (ACF-D), which resemble miniature hyperplastic polyps and adenomas, respectively. They are minute non-polypoid lesions, which may be visualized using low-magnification stereomicroscopy combined with methylene blue staining[34] and *in vivo* utilizing high-magnification chromoendoscopy techniques,[37] which methods have not yet yielded therapeutic implications.

HYPERPLASTIC POLYP

The first morphological descriptions of hyperplastic (metaplastic) polyps are from the late 19th century (reviewed[38]), but the distinction between hyperplastic polyps and adenomas was made by Morson in 1962.[39] Hyperplastic polyps have traditionally been regarded as non-neoplastic lesions, although clustering of hyperplastic polyps and adenomas was known to occur, and in some reports hyperplastic polyps were postulated to be indicators of more advanced neoplasms.[40–43] While adenomatous polyps were documented to progress into carcinoma,[44] such evidence was not found at that time to support the malignant potential of hyperplastic polyps. Later, the genetic explanation of the adenoma–carcinoma model[45] became widely accepted as the dominant model for CRC development. Hence, there was a combination of both morphological evidence and a genetic explanation for the adenoma–carcinoma sequence, while there was no evidence of such behaviour and no need for explanation for hyperplastic polyps. Therefore, it is not surprising that the non-neoplastic nature of hyperplastic polyps developed into an unconditional dogma, one that has been difficult to challenge after having been accepted for several decades.

Hyperplastic polyps have a prevalence of 10–12.5% in asymptomatic patients in large cohort studies.[46,47] They comprise 80–90% of all serrated polyps and they typically locate in the rectosigmoid area, where they are still considered to be innocuous lesions.[8,13,48,49] Proximal hyperplastic polyps differ from distal hyperplastic polyps by their morphology[50] and it is now acknowledged that large and proximal as well as those occurring in the context of hyperplastic polyposis may

represent 'sessile serrated adenomas', which have some malignant potential.[10,11,13,51]

In light microscopy, hyperplastic polyps are small, usually < 5 mm in diameter, symmetrical and uniform. Epithelial serration is confined to the surface and upper part of the crypts and proliferation occurs at the crypt basis. Hyperplastic polyps do not show nuclear atypia apart from some vesicular nuclei. Hyperplastic polyps showing excess proliferation or slight architectural disorganization, not fulfilling the criteria of sessile serrated adenoma, have been observed, but their biological behaviour is unknown.[49] It has been proposed that hyperplastic polyps be classified according their cellular composition into microvesicular, goblet cell and mucin-poor variants (Table 1).[13] Molecular alterations observed in the microvesicular variant may relate it to serrated adenomas, but otherwise it is not known whether these subgroups of hyperplastic polyps differ in terms of clinical behaviour.[52–54]

SESSILE SERRATED ADENOMA

The morphological features for sessile serrated adenoma were originally described in 1996 by Torlakovic and Snover in the context of hyperplastic polyposis,[14] although the original morphological description of serrated adenoma included some of the features of sessile serrated adenoma.[8] The concept of sessile serrated adenoma was reintroduced in 2003, when Torlakovic and colleagues[13] and Goldstein and colleagues[11] described the morphological characteristics of polyps resembling hyperplastic polyps, but with an association of abnormal proliferation and metachronous CRCs showing high-level microsatellite instability (MSI-H). They were accounted to represent 18–22% of serrated polyps,[11,13] but subsequent demographic cohorts have yielded lower numbers (8%).[49] Sessile serrated adenomas represent a morphological intermediate between hyperplastic polyp and serrated adenoma, although this may not be biologically exact, as there are certain differences in their genetic background, such as in the frequency of *BRAF* mutations and CpG island methylation.[17,53,55]

Sessile serrated adenomas have a predilection for the proximal colon, but are distributed throughout the colon and rectum.[11,13,49] Endoscopically sessile serrated adenomas are slightly elevated lesions with irregular borders, and may be covered with mucus.[56,57] Chromoendoscopy studies have shown that they have a pit pattern different from hyperplastic polyps and serrated adenomas.[57–59]

Histopathological diagnosis of sessile serrated adenoma may be difficult, as it bears closer resemblance to hyperplastic polyps than to traditional serrated adenomas, and lacks distinct adenomatous dysplasia.[11,13,18] Sessile serrated adenomas differ from hyperplastic polyps by disorganized architecture, an extended proliferative zone and subtle cellular atypia. Branching crypts, crypt dilation, crypts filled with mucus, inverted T- or L-shaped crypts and crypt invagination beneath the mucosal muscle layer are consistent features. The proliferation zone extends from the crypt basis and cells often have vesicular nuclei with slight chromatin irregularities.[11,13,14] Some of these features have been found in proximal hyperplastic polyps, suggesting a relationship with sessile serrated adenomas.[50] In a recent series, the prevalence of sessile serrated adenomas was shown to be about 1/10 of that of hyperplastic polyps in total, but slightly less than one-third of that of proximal hyperplastic polyps.[49]

ADMIXED POLYP: A SESSILE SERRATED ADENOMA IN PROGRESSION?

Large and proximal hyperplastic polyps have occasionally been reported to contain dysplastic areas[60–62] and they have hence been named mixed hyperplastic/adenomatous polyps or hyperplastic polyp/adenoma.[8,61] It has been hypothesized that admixed polyps represent a collision tumour, or that the adenomatous foci represent a non-serrated adenomatous component.[8] Both of these assumptions may reflect difficulty in the interpretation of high-grade serrated dysplasia, which has been described in detail only recently, describing admixed polyps as immediate successors of sessile serrated adenomas.[12,51,63–65]

Sessile serrated adenoma was originally described as a variant of hyperplastic polyp, and cases representing distinct dysplasia (admixed polyps) were excluded from the definition to distinguish the subtle cellular alterations of these lesions from (traditional) serrated dysplasia,[11,13] which left the relationship of sessile serrated adenomas and admixed polyps an open issue. In a recent series, 96% of admixed polyps were shown to represent low- and high-grade serrated dysplasia, and in only one case (4%) could serrated morphology at the high-grade area not be appreciated.[64] In the same study, the majority (86%) of mixed polyps associated with cancer were located in the ascending colon and were associated with immunohistochemical loss of DNA repair-associated genes *MGMT* and *hMLH1*; 38% of these cancers had serrated morphology, whereas the remaining cases had a more traditional growth pattern. In the study of Mäkinen and colleagues, the serrated adenomatous component adjacent to serrated adenocarcinoma harboured areas of conventional dysplasia

in 33% of cases, and it is probable that some of these cases were sessile serrated adenomas with higher-grade dysplasia, as two-thirds of these were located in the proximal colon.[9]

SERRATED ADENOMA

Serrated adenoma, originally described by Longacre and Fenoglio-Preiser, was considered to be a lesion of minor importance, representing only 0.6% of the vast amount of over 18 000 polyps studied.[8] The impact of serrated adenomas on CRC development was therefore considered to be small, despite the fact that they represented significant dysplasia in over one-third of the cases and intramucosal carcinoma in 11% of cases.[8] The observed prevalence of serrated adenomas has been higher (2–3.5%) in recent reports, which is probably related to improved recognition.[49,66] Serrated adenomas have a predilection for the distal colon and rectum and they usually have more a pedunculated or broad-based polypoid growth pattern than sessile serrated adenomas, with a cerebriform or flower-petal-like endoscopic appearance.[57,67]

In traditional serrated adenomas, dysplasia is usually readily apparent, with nuclear stratification and penicillate nuclei combined with abundant to moderate eosinophilic cytoplasm. Serrated glands form star-shaped slitted luminal spaces. Serrated adenomas have shown to be neoplasms with high proliferative capacity, with a tendency for development into higher-grade neoplasms.[63,68,69] Recent reports have claimed that serrated adenomas have a higher growth rate than adenomatous polyps and that the subsequent cancer risk rate at least equals that of adenomatous polyps.[63,70]

HYPERPLASTIC POLYPOSIS AND HYPERPLASTIC POLYPS IN OTHER POLYPOSIS SYNDROMES

Hyperplastic polyposis is a preneoplastic condition, where multiple hyperplastic polyps occur throughout the colon.[14,38] CRC risk may be over 50% and multiple synchronous or metachronous cancers may occur.[71–79] These are usually MSI-H[76] and present with a serrated morphology.[75,77] World Health Organization criteria for hyperplastic polyposis include (i) ≥ 30 hyperplastic polyps proximal to sigmoid colon, (ii) over five polyps proximal to sigmoid colon, more than two of which are >10 mm, and (iii) any number of hyperplastic polyps proximal to the sigmoid colon, if the patient has a first-degree relative with hyperplastic polyposis. Hyperplastic polyps in hyperplastic polyposis differ from isolated hyperplastic polyps[14] and these criteria also apply to most sessile serrated adenomas.[11,13,20,22]

An excess of hyperplastic polyps and serrated adenomas may be found in familial adenomatous polyposis (FAP) patients[80] and the latter may represent part of the disease spectrum.[81] In hereditary non-polyposis colorectal cancer (HNPCC), serrated adenomas are rare[82] and hyperplastic polyps do not usually exhibit MSI or loss of MLH1 in immunohistochemistry.[83] Serrated adenoma has been associated with Cronkhite–Canada syndrome[84] and serrated epithelial proliferation with unknown biological significance may occur in juvenile polyps[38] and in solitary rectal ulcer syndrome.[85]

ASSESSMENT OF DYSPLASIA IN SERRATED ADENOMAS

By definition, adenomatous polyps harbour dysplasia and, similarly, hyperplastic polyps have traditionally been thought not be dysplastic. Through decades of training, pathologists are comfortable with detecting dysplasia in adenomas and are equally hampered in detecting dysplasia in serrated polyps, especially in the case of sessile serrated adenoma. The nature of dysplasia in serrated lesions, however, differs from that of adenomatous polyps, as serrated adenomas are frequently characterized by mature, eosinophilic or clear epithelium with a low nuclear–cytoplasmic ratio.[63,86,87] Lazarus *et al.* proposed histological criteria for serrated dysplasia that distinguished the polyps with an increased risk of metachronous lesions, but their classification did not distinguish sessile serrated adenomas from serrated adenomas.[63] Whether such a distinction is clinically relevant is not yet known. As sessile serrated adenoma represents more architectural irregularities than evident cytological dysplasia, the diagnostic features of serrated dysplasia should probably be reappraised.[10–13,22,23,51,63]

Risk factors

Serrated adenocarcinoma and its precursor lesions have not yet been treated as separate entities in epidemiological studies and therefore their aetiological and risk factors remain hypothetical. However, hyperplastic polyps and conventional adenomas share the same recognized risk factors and it is likely that the factors behind serrated adenomas are rather similar. Smoking, alcohol intake, high body mass index (BMI) and low fibre intake increase the risk for adenomas and hyperplastic polyps, whereas frequent non-steroidal anti-inflammatory drug use, hormone replacement therapy and dietary calcium and folate supplements have a protect-

ive effect.[88–90] The magnitude of the risk may vary, and heavy smoking and high BMI have been shown to result in a greater risk of hyperplastic polyps.[91]

Dietary folate supplements and oestrogen are two interesting protective factors and a decrease in their blood concentrations may be involved in the serrated route. Dietary folate is required for purine synthesis, but it is also involved in DNA methylation in the methylation cycle.[92] Inadequate dietary folate supply has been associated with systemic DNA hypomethylation as well as an increased risk of hyperplastic polyps and CRC.[88,92,93] Genetic variation in folate metabolism may also play a role in the serrated neoplasia pathway, since proximal CRCs with a so-called CpG island methylator phenotype (CIMP) have been associated with polymorphism of methylenetetrahydrofolate reductase enzymes.[94,95] Likewise, endo- and exogenous oestrogens may have a similar impact on the development of serrated neoplasms, since oestrogen withdrawal, either by menopause or by iatrogenic causes, increases the risk of microsatellite unstable CRC in women.[96] Recently, the JC virus has been postulated to be involved in the development of CRC and to be associated with CpG island methylation.[97]

Cancer risk

The cancer risk of patients with serrated adenomas is beyond doubt. There are several reports with supporting evidence, including (i) malignant progression of lesions originally considered to be hyperplastic polyps,[61,62,72,73,75,98] (ii) CRC associated with hyperplastic polyposis,[61,62,72,73,75,77,98,99] (iii) recognition of dysplasia in serrated adenoma and sessile serrated adenoma,[8,11,13,14,51] (iv) metachronous cancers and serrated adenomas associated with serrated adenomas or lesions originally considered to be hyperplastic polyps,[11,63,100,101] (v) serrated adenomas being adjacent to or surrounding carcinomatous tissue,[9,51,64,77,82,101–104] (vi) morphological and immunohistochemical similarity of some cancers to hyperplastic polyps and serrated adenomas,[9,77,101,103–107] (vii) common mutations and epigenetic alterations in the various stages of the serrated pathway, including oncogenic *BRAF* and *KRAS*, concordant DNA hypermethylation and DNA microsatellite instability[31,52,54,108–111] and (viii) distinct clustering of CRCs with serrated morphology analogous to serrated adenomas in DNA array analysis.[112]

While the malignant progression of serrated polyps has been well documented, the magnitude of cancer risk of patients with serrated polyps is less well characterized. Sporadic tubular adenomas are frequent, and only a small proportion of sporadic conventional adenomas become malignant.[113] In contrast, most untreated adenomas in HNPCC patients may become malignant over time.[114]

There have been a number of arguments favouring the idea that serrated adenomas are also highly likely to become malignant.[10,115] Serrated adenocarcinomas have a higher prevalence than serrated adenomas[49,51,104] and patients with serrated adenomas had a high propensity for metachronous serrated adenoma (26%) or synchronous cancer (19.6–24%).[70,116] High-grade serrated adenomas have been associated with rapid recurrence and, ultimately, the development of serrated adenocarcinoma in a few case reports[101,117] and metachronous CRC has been observed in 5.3% of patients with serrated adenomas, in contrast to 2.2% of patients with conventional adenomas.[63] The risk of malignant progression in sessile serrated adenomas is construed from the ratio of the reported frequencies of right-sided sessile serrated adenomas and MSI-H cancers, and from the risk of metachronous lesions in patients with serrated adenomas.[9,10,63,100,118]

In one recent demographic series, advanced serrated polyps (sessile serrated adenomas, admixed polyps and serrated adenomas) accounted for 4.9% (61/1250) of all colorectal polyps and 17% of all serrated polyps.[49] In that study, 6.4% of proximal lesions were advanced serrated polyps and 79.1% were adenomas,[49] whereas the frequency of serrated adenocarcinomas in the proximal colon has been reported to be 12%.[104] On this premise, it is possible that all serrated adenomas with noticeable dysplasia have a higher tendency for cancer development than conventional adenomas. As the relative cancer risks of sessile serrated adenomas, admixed polyps and serrated adenomas are not yet well established, it may be possible that the reported series has classified both low-risk and high-risk serrated polyps under the same categories.[63] It is therefore possible that high-grade polyps have an even higher risk of malignant progression than anticipated.

It has also been also suggested that serrated adenocarcinomas may develop and grow faster than non-serrated, sporadic CRC.[115] This hypothesis is based on an analogy to HNPCC, where faster growth rate and development of interval cancers has been related to the presence of MSI-H.[5,7] It has been assumed that sporadic MSI-H cancers behave similarly. There are a few reports supporting this suggestion.[101,117] While the diminished apoptosis seen in serrated adenomas may favour this suggestion, it has been estimated that sporadic MSI-H cancers have a lower growth rate than

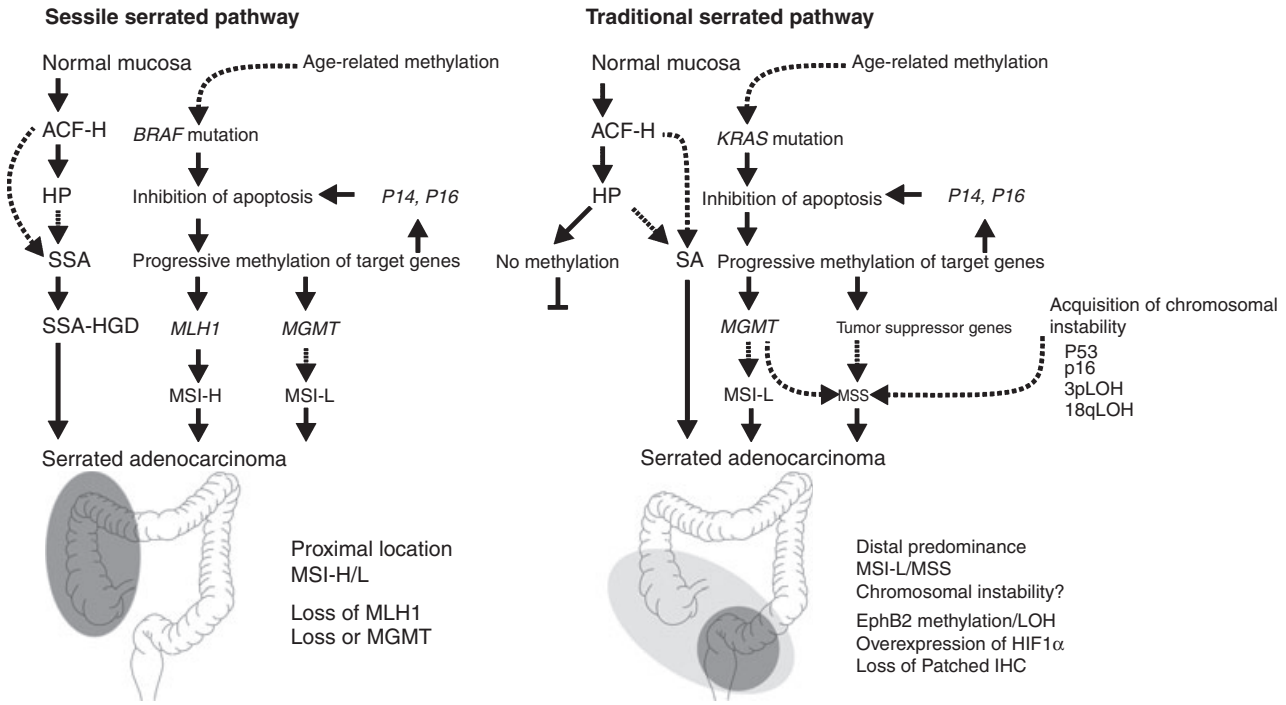


Figure 1. Schematic expression of the putative sessile and traditional serrated pathways. Solid lines represent documented and dotted lines the putative sequence of alterations. HGD, high-grade dysplasia; IHC, immunohistochemistry.

HNPCC cancers[119] and that serrated adenocarcinomas do not differ from non-serrated cancers.[69]

Molecular alterations in serrated pathway lesions

The development of serrated neoplasia (Figure 1) has been associated with three frequent alterations, which have a certain analogy to the adenoma–carcinoma sequence of the adenoma–carcinoma model. These alterations include: (i) activation of mitogen-activated protein kinase-extracellular signal-regulated kinase (MAPK–ERK) signalling pathway, (ii) inhibition of apoptosis, and (iii) abnormal silencing of certain genes by DNA methylation, with ensuing DNA MSI. These events have been shown to be causally associated, analogous to the adenoma–carcinoma sequence.

The recognition of serrated pathway lesions stems from the discovery of MSI. Of sporadic CRCs, 10–15% show MSI and these have been associated with serrated morphology,[9,82,100,120–122] an aberrant methylation pattern involving methylation of *hMLH1* or *MGMT* genes[64,108,110,123–126] and *BRAF* mutations.[108,110,124,125] Sessile serrated adenomas have therefore been claimed to represent precursor lesions for these cancers, as they harbour a similar profile of alterations.[12,16,51,55,82,104,121,122,127,128]

MAPK–ERK PATHWAY

The earliest genetic alterations in serrated lesions are *BRAF* and *KRAS* mutations, which are observed in aberrant crypt foci.[31] K-Ras and B-Raf are participants of the MAPK–ERK pathway, which is an important pathway which mediates cellular responses to many extracellular signals regulating cell growth, differentiation and apoptosis. *KRAS* and *BRAF* mutations are mutually exclusive in most colorectal polyps and in CRC,[129] which indicates that both mutations occur early in neoplasm development and also supports the idea that there are two parallel serrated pathways that rarely cross over. This hypothesis is supported by the notion that *KRAS* and *BRAF* mutations segregate the type of lesion. *KRAS* mutations, common in polypoid and rare or absent in flat adenomas and cancers,[130–132] are harboured by 3–17% of colorectal adenomas and up to 40% of CRCs harbour *KRAS* mutations.[133–135]

In serrated lesions, *KRAS* mutations are found in up to 82% of ACF-H,[136,137] while they are less frequently (about 4–37%) found in hyperplastic polyps.[52,65,65,110,111,138–141] Prior to the recognition of sessile serrated adenoma, various reports yielded conflicting results on the frequency of *KRAS* mutations in serrated adenomas.[139,142,143] This paradox was

probably resolved when it was found that *KRAS* mutations are very common (80%) in rectal and polypoid (traditional) serrated adenomas, but rare in sessile serrated adenomas (0–10%).[52,53,65,110,143]

In contrast, *BRAF* mutations are rare in sporadic ACF-H and in hyperplastic polyps,[31] but very frequent in sessile serrated adenomas (75–82%), in admixed polyps (40–89%)[65,144] and in lesions associated with hyperplastic polyposis.[31] The reported frequencies in hyperplastic polyps and serrated adenomas are lower (19–36% and 20–33%, respectively).[65,110,111] It has been hypothesized that *KRAS* mutations in ACF-H and hyperplastic polyps may not be sufficient for neoplastic progression, which may require more associated alterations, such as methylation, whereas ACF-H with *BRAF* mutations has sufficient propensity for neoplastic progression.[55]

The most common *BRAF* mutation (V600E, formerly V599E) results in a constitutively activated enzyme.[129] It has been identified in 5–15% of CRCs and is strongly associated with DNA methylation and MSI.[108,110,145,146] The high frequency of *BRAF* mutations in sessile serrated adenomas is surprisingly similar to the 76% incidence reported for MSI-H CRC[110,125] and in sharp contrast to the 0% incidence of *BRAF* mutations in HNPCC cancers.[125] This also lends strength to the notion that most sporadic MSI-H CRCs originate from sessile serrated adenomas.[125,147,148]

In addition to *BRAF* and *KRAS* mutations, another recently documented alteration associated with the MAPK–ERK pathway in serrated adenocarcinoma is down-regulation of *EPHB2*. EphB2 belongs to the large family of Eph receptor tyrosine kinases. Eph receptors are membrane proteins that are important regulators of the spatial organization of various cells in tissues. In intestinal epithelial cells, EphB2 and EphB3 determine the direction of cellular differentiation in the crypt villus axis by down-regulating the MAPK pathway via Ras and Raf.[149,150] Disruption of *EphB2* and *EphB3* genes in the knockout mouse model leads to disorganization of both growth directions of the crypt epithelium and to abnormal mixing of cell types.[150] EphB2 down-regulation is thought to result in sustained activation of the MAPK–ERK pathway, analogous to that of activated forms of K-Ras and B-Raf. *EPHB2* is located at 1p36, which has been reported to be lost in 13% of hyperplastic polyps in hyperplastic polyposis.[151] *EPHB2* is methylated in 63% and shows loss of heterozygosity (LOH) in 25% of serrated adenocarcinomas, and is accompanied by loss of EphB2 immunohistochemistry in $>80\%$ of cases.[112] While *EPHB2* is a novel and important gene frequently altered in serrated adenocarcinomas, its role in early serrated lesions needs to be determined.

ALTERATIONS IN THE REGULATION OF APOPTOSIS

Inhibition of apoptosis occurs frequently in the serrated pathway. It is thought to be a consequence of oncogenic *BRAF* and *KRAS* mutations and to be behind the convoluted serrated morphology.[25,26] Activation of anti-apoptotic signalling of B-Raf in serrated polyps occurs via MEK.[152] Inhibition of apoptosis occurs via oncogenic B-Raf and is also observed in cells with *KRAS* codon 12 mutations.[133] Such serrated polyps, where *BRAF* or *KRAS* mutations would result in proapoptotic signalling, probably regress, which has been reported to occur in hyperplastic polyps.[153,154] It has been suggested that the inhibition of apoptosis in serrated polyps results in an increase in methylation, as older cells may harbour more methylated sites,[23] and that early serrated polyps represent a 'safe haven', where more genetic alterations are allowed to occur without cells being signalled to undergo apoptosis. Diminished apoptosis and increased methylation may represent a vicious cycle in serrated polyps, since excess methylational silencing of apoptosis-associated genes, such as *P14* and *P16*, is frequent in serrated polyps and in CRCs presenting with excessive methylation.[103,125] Inhibition of apoptosis seems to be sustained in serrated adenomas in comparison with conventional adenomas,[25,68,69,155] but this difference disappears during malignant conversion, as the apoptosis:proliferation ratio in serrated adenocarcinomas does not differ from non-serrated adenocarcinomas.[69]

ABNORMAL METHYLATION

DNA methylation is essential for many epigenetic mechanisms used in gene regulation, such as DNA imprinting, X-chromosome inactivation and controlling tissue-specific gene expression.[156,157] DNA methylation by formation of 5-methylcytosine from cytosine occurs at enriched, repetitive CG sequences (CpG islands), which at the location of DNA promoter regions may result in gene silencing.[156] In cancer, disturbances in DNA methylation are seen in two forms, i.e. as hypermethylation of DNA promoter regions of certain genes, and as global hypomethylation.[158,159] These two mechanisms seem to be unrelated[160] but there is evidence that both might be related to deficient folate intake[92,161] and that these alterations are at least partially reversible when folate intake is restored.[93,162]

Excess of methylation has been observed in about 30–50% of CRCs, is referred to as CIMP and has been divided into low-level (CIMP-L) and high-level

(CIMP-H) type, which have been detected with variable frequencies.[52,53,110,163–167] This is likely to be related to the markers used, and a recently introduced, improved marker panel has associated CIMP almost one-to-one with *BRAF* mutations.[108]

In the serrated pathway, increased methylation is an early phenomenon[166] and it has been detected in small hyperplastic polyps, ACF[31] and even in the normal mucosa of the proximal colon from patients with hyperplastic polyposis[109] and in the mucosa from patients with CRC.[168] The consequences of methylation depend on the target genes involved. Genes frequently involved in the serrated pathway include *MLH1* and *MGMT*, which are associated with high- and low-level MSI, respectively, apoptosis-associated genes *P14* and *P16*, and *EPHB2*,[53,64,82,103,112,125,126,169–171] suggesting that most cancers developing from serrated adenomas develop via aberrant methylation.[17,103]

MICROSATELLITE INSTABILITY

Microsatellite instability was first found in association with HNPCC, where germ-line mutations of mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6* and, rarely, *PMS2* result in high-level MSI in over 90% of cases.[172–176] In sporadic CRCs, MSI-H is nearly always associated with *MLH1* methylation, while methylation of other MMR genes is very rare.[82,124,127] MLH1 methylation has been detected in 36% of hyperplastic polyps, 70% of sessile serrated adenomas and 86–87% of sporadic MSI-H CRCs.[17,82,125] Loss of MLH1 immunohistochemistry has not been detected in hyperplastic polyps or traditional serrated adenomas,[11,64,177] but is seen in over 27% of sessile serrated adenomas.[11] These findings are in accord with the notion that sessile serrated adenomas are frequent precursors of sporadic MSI-H CRCs.

In contrast, background events for low-level MSI (MSI-L)[178] are less evident and MSI-L has not been associated with alterations in MMR genes: it is a quantitative rather than qualitative phenomenon, as a lesser degree of MSI has been detected when more markers have been used.[179–181] However, methylation of the DNA repair gene *O6-methylguanine-DNA methyltransferase* (*MGMT*) has been indicated in the serrated pathway. It has been postulated that deficient MGMT results in an override of the MMR system, resulting in the acquisition of MSI-L.[17,103,126] MGMT methylation is rare (6%) in HNPCC,[125] but has been detected in 22% of hyperplastic polyps,[53] in 24.6% of sessile serrated adenomas,[53] in 16–22% of serrated adenomas with a variable degree of dysplasia[103] and in 50% of serrated adenocarcinomas[103] and may occur with hMLH1 methylation in 20% of sporadic MSI-H cancers.[125] The observed 29.7% frequency of MSI-L in serrated adenocarcinomas contrasts with 13.7% of MSI-L in non-serrated adenocarcinomas,[104] favouring the suggestion that factors inducing MSI-L are important for the development of serrated neoplasms. The high frequency of microsatellite stable (MSS) serrated adenocarcinomas underlines the concept that the significance of MSI-L itself has not yet been determined in the serrated pathway.

OTHER MOLECULAR ALTERATIONS

In addition to recent *BRAF*/KRAS mutations and DNA methylation, serrated adenomas have been shown to harbour frequent *p53* mutations,[142] infrequent *APC* mutations or LOH of 5p and frequent allelic imbalance of 18q.[141,142,182] Chromosomal losses or gains have usually been associated with MSI-L and MSS serrated adenomas, while being rare in MSI-H cancers.[121,183–186] These alterations include infrequent LOH of 3p, 5q, p53 and p16, and gains of 8q and 13q.[181,183,184]

Serrated adenocarcinoma

The discovery of serrated adenocarcinoma was anticipated by the recognition in several studies of high-grade dysplasia or intramucosal carcinoma within serrated adenoma.[8,51,57,102,139,142] Serrated adenocarcinoma was first described by Jass and Smith[105] and, to date, over 80 colorectal adenocarcinomas arising from serrated adenomas or large hyperplastic polyps have been described in the reported series.[9,51,63,72,75,77,82,101,104,104,105,112,117,142,187–190]

Serrated adenocarcinoma is an end-point of the serrated neoplasia pathway and has been recognized as a distinct entity among CRCs, accounting for 7.5% of them.[104] The majority of serrated adenocarcinomas are MSS or MSI-L and originate from traditional serrated adenomas,[103,104] whereas 17% of serrated adenocarcinomas may originate in sessile serrated adenoma, frequently presenting with MSI-H.[51,104] Thus, it may be biologically relevant to distinguish serrated adenocarcinomas according to their precursor lesions.[30,104,128,183]

Clinical and pathological characteristics

GENDER

Serrated adenocarcinomas represent 9.3% of all CRCs in females and 5.8% in males, based on two previous studies.[9,104] In females, over 18% of adenocarcinomas

of the ascending colon and caecum are serrated adenocarcinomas. While both sessile and traditional serrated adenomas are more common in males, serrated adenocarcinomas have an opposing male:female ratio of 1.9 : 1.[104] The reason why women apparently have a higher risk of malignant conversion of serrated adenoma is not known, the possible explanation remaining speculative. Sporadic MSI-H carcinomas are more frequent in women, occur at an old age and often have a serrated morphology.[82] As oestrogen withdrawal and folate depletion have been shown to induce both MSI and CpG methylation and result in an increased cancer risk, it is possible that serrated lesions appearing in women prior to menopause may have a higher risk of malignant conversion after menopause than lesions in men during the same time span, owing to oestrogen withdrawal and a drop in folate levels. If this explanation can be verified, then it may become even more necessary to prompt complete removal and close follow-up of sessile serrated adenomas in women.[22]

Table 2. Definition of the criteria used in the evaluation of serrated adenocarcinoma[104]

1. Epithelial serrations Includes: epithelial tufts composed of only epithelium or epithelium and basement membrane material
Excludes: papillary projections with a fibrovascular core and serrated-like structures resulting from tumour cell necrosis
2. Clear or eosinophilic cytoplasm
3. Abundant cytoplasm
4. Vesicular nuclei Chromatin condensation at the nuclear envelope, accompanied by abundant amount of euchromatin
5. Discernible nuclei A subjective observation about combined pattern of abundant, eosinophilic or clear cytoplasm and chromatin condensation at the nuclear envelope
6. Absence of necrosis*
7. Mucin production
8. Cell balls and papillary rods

*89% of serrated adenocarcinomas were completely devoid of necrotic areas, with the remaining 11% focal necrotic areas not comprising more than 10% of the total surface area. This was contrary to the conventional carcinomas, where only 26% of cases were devoid of necrotic areas.[104]

LOCATION

Up to 16% of adenocarcinomas of the caecum and ascending colon are serrated adenocarcinomas, whereas in the distal colon and rectum they make up slightly less than 6% of all cancers.[104] In the original series by Mäkinen and colleagues,[9] serrated adenocarcinoma was observed predominantly in two locations: 52% of the cancers were observed in the caecum and 33% in the rectum. While this difference in localization was difficult to interpret at the time, it is now conceivable that many proximal serrated adenocarcinomas are related to sessile serrated adenomas and that most distal serrated adenocarcinomas have their origin in traditional serrated adenomas, since sporadic MSI-H carcinomas, MSI-H serrated adenocarcinomas and sessile serrated adenomas all share proximal localization, whereas traditional serrated adenomas, MSI-L and MSS serrated adenocarcinomas have a predilection for the distal colon and rectum, but are more uniform in their distribution.[104]

MORPHOLOGY

The morphological criteria for serrated adenocarcinoma have been described recently, based on cases where serrated adenoma was adjacent to adenocarcinoma (Tables 2 and 3).[104] Most histopathological features of serrated adenocarcinomas have been described as features of sporadic MSI-H cancers.[127,191] These include: (i) serrated morphology,[82] (ii) mucinous differentiation in association with *BRAF* mutations,[123,192,193] (iii) cell clusters or chains floating in mucin,[194] (iv) eosinophilic cytoplasm,[195] (v) vesicular nuclei[195] and (vi) the absence of dirty necrosis.[196]

These findings are in line with the hypothesis that many sporadic MSI-H cancers are serrated adenocarcinomas. However, only 16% of serrated cancers are MSI-H, and as these features are consistently seen in MSI-L and MSS serrated adenocarcinomas, I would argue that they are features of serrated adenocarcinoma, rather than a result of DNA MSI.[104] Serrated morphology has been demonstrated in a few cases of MSI-L cancers,[121] but it is likely that serrated morphology in MSS cancers has not been appreciated in most studies.

Some authors have suggested that most sporadic MSI-H cancers develop from sessile serrated adenomas, and that they might also have a non-serrated morphology, including a medullary, mucinous or mixed pattern, and present with prominent lympho-

Table 3. Distinguishing histopathological features between serrated and non-serrated carcinoma[104]

	Serrated adenocarcinoma	Non-serrated carcinoma
Adjacent adenoma if present	Serrated adenoma	Tubular adenoma
	Sessile serrated adenoma	Tubulovillous adenoma
		Villous adenoma
Major growth pattern (> 75% of the surface area)	Serrated (71%)	Tubular or papillary (71%)
	Mucinous (17%)	Cribriform (18%)
	Trabecular* (7%)	
Serrated or papillary structures	Epithelium only (36%)	Epithelium with fibrovascular core (49%)
	Epithelium and BM (57%)	No serrations (43%)
	No serrations* (7%)	
Cytoplasm	Eosinophilic (93%)	Basophilic or amphophilic (69%)
	Clear (7%)	Eosinophilic (31%)
Nuclear–cytoplasmic ratio	Low (57%)	High (69%)
	Moderate (39%)	Moderate (26%)
	High (4%)	Low (4.1%)
Necrosis	Absent (89%)	> 10% of surface area (52%)
	< 10% of surface area (11%)	< 10% of surface area (22%)
Mucin production (% of surface area)	< 20% (34%)	< 20% (78%)
	20–50% (23%)	20–50% (15%)
	> 50% (43%)	> 50% (7%)
Cell components in mucinous carcinomas	Papillary rods (93%) Cell balls (79%)	No papillary rods (80%) No cell balls (80%)

*Trabecular growth pattern.
BM, Basement membrane.

cytic infiltrate.[118] These tumours may also represent serrated adenocarcinomas, which are often mucinous, and poorly differentiated serrated adenocarcinomas may show a non-serrated trabecular growth pattern.[104] MSI-H has been detected in 16.1% of serrated adenocarcinomas and 80% of them were located in the proximal colon.[104] This is consistent with the concept that sessile serrated adenomas represent the precursors of MSI-H proximal cancers. Indeed, in the report of Tuppurainen *et al.*, 17% of serrated adenocarcinomas had an adjacent sessile serrated adenomatous component with cellular atypia being surprisingly mild.[104]

Tuppurainen and colleagues have recently refined the histopathological criteria for serrated adenocarcinomas (Tables 2 and 3) and they have also tested the reproducibility of these criteria.[104] Five pathologists were able to achieve a moderate overall interobserver agreement ($\kappa = 0.583$) after a short training period.[104] The validity of this classification has also been shown by distinct molecular clustering of serrated adenocarcinomas classified using these criteria,[112] signifying that serrated adenocarcinoma is a genuine entity and that morphological features associated with serrated adenocarcinomas are both reproducible and biologically relevant.

Three major growth patterns are associated with serrated adenocarcinoma: serrated pattern, trabecular pattern and mucinous pattern (Figure 2).[104] The serrated pattern is encountered most frequently, representing over two-thirds of serrated adenocarcinomas. Epithelial serrations consisting of epithelium or epithelium and basement membrane (BM) structures are even more frequent, and are seen in most cases (93%). The mucinous pattern overlaps with the serrated pattern, as 43% of serrated adenocarcinomas are mucinous and 23% have a mucinous component. Paucity of serrations, resulting from the distension of the mucus, is rare, however. The trabecular pattern is characteristic of poorly differentiated serrated adenocarcinomas (7%) that may lose their ability to form serrated structures, but these cases still frequently show an eosinophilic, relatively abundant cytoplasm with vesicular nuclei and chromatin condensation at the nuclear envelope.

Nearly 90% of serrated adenocarcinomas are devoid of any necrotic areas and in the remaining cases, necroses are minimal or focal, comprising no more than 10% of the surface area. In contrast, conventional carcinomas exhibit necrotic areas in three-quarters of the cases, and cribriform growth pattern frequently shows central necrosis, which may result in an appearance simulating serrations.[104] In such cases, the presence of necrosis does not favour the diagnosis of serrated adenocarcinoma.

SERRATED PATTERN

The serrated growth pattern is retained in well and moderately differentiated serrated adenocarcinomas (Figure 2a,c,d) and may be seen focally in poorly differentiated serrated adenocarcinomas with either a mucinous or trabecular growth pattern. Serrated-pattern epithelium is mature, abundant, eosinophilic or clear, often mucus-producing epithelium, and has well-preserved polarity. The epithelium usually has a close resemblance to serrated polyps (Figure 2b). In some cases, serrations may be exaggerated and form long, slender papillary structures, which have been described as pseudocribriform serrations.[8,9] Epithelial serrations are composed of epithelium and possibly BM material, but lack the fibrovascular cores seen in non-serrated carcinomas. It is noteworthy that non-serrated adenocarcinomas, which form complex tubular or cribriform structures, often undergo central necrosis. As a result, the remaining epithelium forms protrusions that may resemble serrations. Cellular features, such as basophilia, poor polarity and high nuclear–cytoplasmic ratio, as well as the presence of central necrosis, speak strongly against serrated adenocarcinoma.

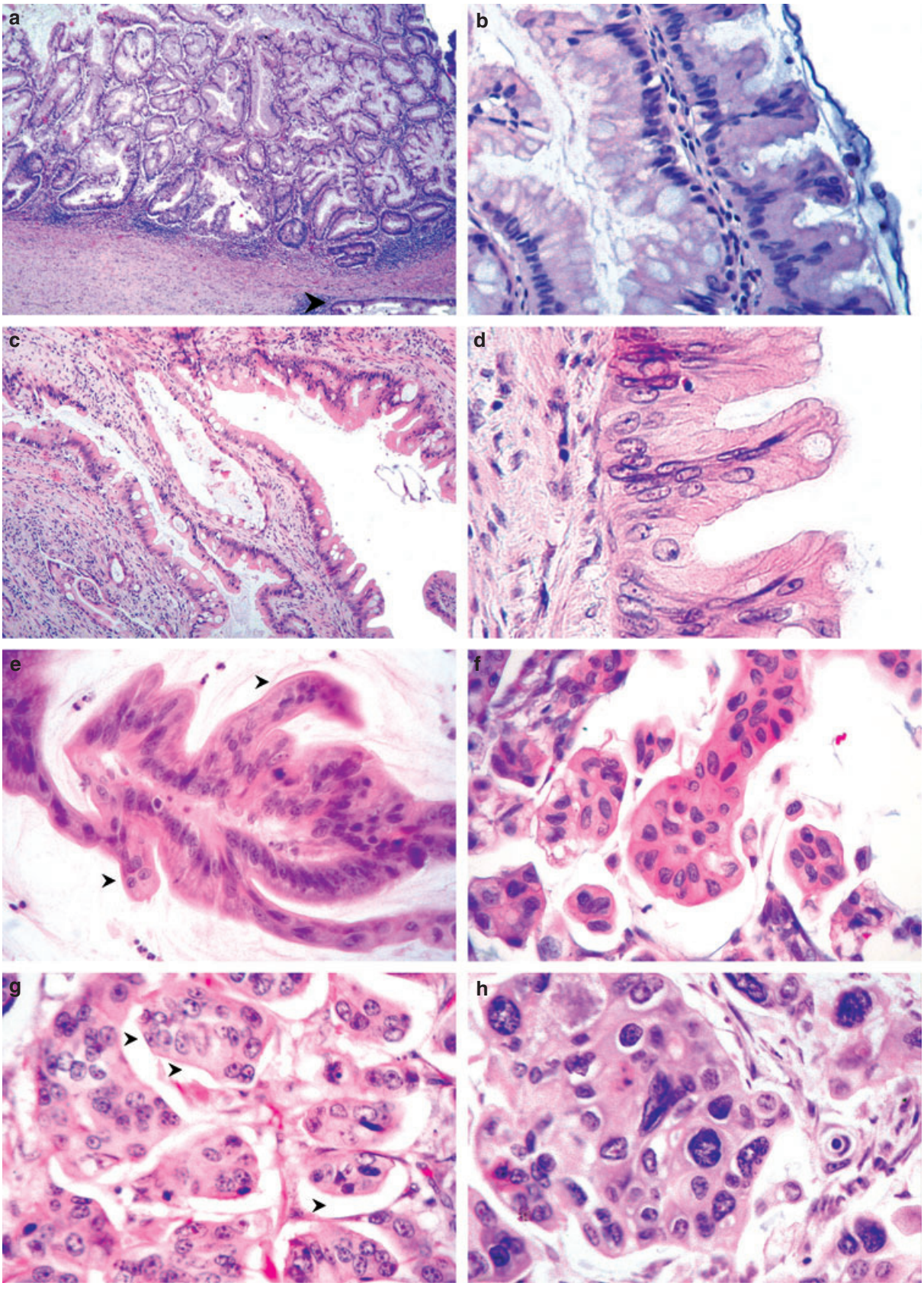
MUCINOUS PATTERN

Mucinous differentiation is very common (43%) among serrated adenocarcinomas, and mucinous pattern serrated adenocarcinomas constitute at least 17.6% of mucinous carcinomas.[9] It is possible that the real frequency is even higher, judged by the concentration of *BRAF* mutations and CIMP among mucinous cancers.[123,197] It may therefore be necessary to re-evaluate mucinous CRCs, as they may represent two entities with potentially different behaviour.

In most mucinous serrated adenocarcinomas, the serrated growth pattern is usually well presented (Figure 2e), but in a few cases epithelial displacement may compress the epithelium so that the serrated projections are not apparent, or an abundance of mucus in combination with poor differentiation may make the serrated pattern illegible. In mucinous serrated adenocarcinomas, 93% present with peculiar eosinophilic papillary rods and 79% with eosinophilic cell balls floating in the mucus (Figure 2f). A combination of distinct cellular features, i.e. eosinophilia, vesicular nuclei and abundance of cytoplasm, is almost invariably present and is sufficient to justify a diagnosis of serrated adenocarcinomna, or at least the statement that the findings are consistent with those of serrated adenocarcinoma.

TRABECULAR PATTERN

In poorly differentiated serrated adenocarcinomas, the serrations subside and the cancer cells grow in a trabecular fashion. There may be actual areas with small slit-like luminal spaces, giving a hint of serrations (Figure 2g), but in some cases the cells form clusters divided by delicate stroma (Figure 2h). This growth pattern may bear some morphological resemblance to invasive micropapillary carcinoma.[198] Poorly differentiated serrated adenocarcinomas may show extensive lymphatic invasion, and it has frequently been observed that the invading border zone in cancers with serrated morphology is often poorly differentiated.[105] In the absence of more differentiated, serrated areas, diagnosis may be difficult, but even poorly differentiated serrated adenocarcinomas show abundant eosinophilic epithelium with vesicular nuclei—features which would rarely be expected in the case of poorly differentiated conventional carcinoma.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CONSOLIDATION OF THE ENTITY: EXPRESSION PROFILE

The validity of the morphological criteria for serrated adenocarcinoma has recently been proved by DNA expression analysis with 7928 probes.[112] The expression analysis showed a distinct clustering of serrated cancers apart from non-serrated cancers, as all but one of the eight serrated adenocarcinomas clustered in a single branch in the hierarchical structure. These results are convincing, and they clearly show that serrated adenocarcinoma is a distinct form of CRC. The expression analysis also yielded over 200 differentially expressed genes[112] and provides a source of potential markers that could be used in developing strategies for the diagnosis, treatment and prevention of serrated adenocarcinoma.

Laiho and colleagues have discovered three new potential candidate genes that may be involved in the serrated pathway: *EPHB2*, *PTCH* and *HIF1α*.[112] EphB2 participates in the intestinal crypt–villus axis differentiation and in polyp formation by inducing neoplastic cell migration away from non-neoplastic cells.[150,199] In non-serrated CRCs, loss of EphB2 is related to advancing stage,[200] but serrated adenocarcinomas are characterized by uniform loss of EphB2.[112] Patched (PTCH) is a transmembrane molecule involved in the Sonic hedgehog (Shh) signalling pathway, which is involved in the spatial organization of cells during organogenesis.[201,202] The constituents of the Shh signalling pathway are expressed in colorectal mucosa, in hyperplastic polyps and in colorectal adenomas and cancer,[203] but *PTCH* expression is diminished in serrated adenocarcinoma compared with non-serrated cancer.[112] Hypoxia-inducible transcription factors (HIF) are heterodimers of HIFα and HIFβ subunits.[204] HIFα is expressed during hypoxia to restore oxygenation and/or energy balance.[204,205] Constitutive overexpression of HIFα provides a growth advantage for solid tumours via vascular endothelial growth factor induction[206] and is associated with the Wnt/β-catenin pathway in colorectal carcinogenesis.[207] HIF1α is constitutively overexpressed in serrated as opposed to non-serrated CRCs[112] and may therefore be important in the serrated neoplasia pathway.

The report of Laiho and colleagues is invaluable in connecting the genetic profile and morphological features of serrated adenocarcinoma and identifying several potential biological markers for serrated adenocarcinoma. Immunohistochemistry against EphB2, HIF1α and Patched might prove useful in the detection of the serrated adenocarcinoma in problem cases,[112] but corroborating studies are needed, since the material in the expression analysis contained only one MSI-H serrated adenocarcinoma (12.5%); this corresponds to the reported 16.1% frequency of MSI-H in serrated adenocarcinomas,[104] but may limit the interpretation of the expression analysis data in determining the biology of the cancers with putative origin in a sessile serrated adenoma.

Prognosis

There is both direct and indirect evidence showing that serrated adenocarcinomas may have an outcome different from that of non-serrated adenocarcinomas. In the study of Mäkinen *et al.*,[9] the cumulative 5-year survival rate of patients with proximal serrated adenocarcinomas was > 70%, whereas it was < 30% in patients with distal serrated adenocarcinomas. In the study of Laiho *et al.*,[112] an extended set of serrated adenocarcinomas (mostly MSI-L/MSS cancers) showed a less favourable prognosis than non-serrated adenocarcinomas matched with sex, age and grade. A major proportion of proximal MSI-H cancers are considered to arise from sessile serrated adenomas and these cancers seem to have an excellent prognosis, whereas distal serrated adenocarcinomas more often show an MSI-L or MSS phenotype, showing a less favourable outcome compared with non-serrated and proximal cancers.[112] On this basis, it is reasonable to suggest that it may be important to distinguish sessile serrated adenomas and traditional serrated adenomas, since their associated malignancies are likely to have different prognoses. This may be reflected in an observation that while *BRAF* mutations have been shown to be frequent in

Figure 2. Typical growth patterns of serrated adenocarcinoma and associated adenoma. **a,** A case of sessile serrated adenoma and associated adenocarcinoma (arrow). **b,** Higher magnification from upper right corner of **a** shows sessile serrated adenoma with well-preserved polarity, abundant cytoplasm and basal nuclei. **c,** Another case of serrated adenocarcinoma shows infiltrative serrated structures. **d,** Higher magnification from lower right corner of **c** shows well-differentiated serrated adenocarcinoma with very mild nuclear atypia and well-preserved polarity. The resemblance to benign serrated polyp is remarkable. **e,** A case of mucinous serrated adenocarcinoma shows epithelium compressed by the mucus, but serrations are still present (arrow). **f,** An area of mucinous serrated adenocarcinoma shows eosinophilic cell balls and a rod-like structure. **g,** A poorly differentiated serrated adenocarcinoma shows trabecular growth pattern combined with eosinophilic cytoplasm, with slit-like spaces (arrow). **h,** Another example of poorly differentiated serrated adenocarcinoma shows trabecular growth pattern and high-grade nuclei, but relatively abundant cytoplasm, discernible nuclei, and light cytoplasmic eosinophilia.

both sessile and traditional serrated adenomas, MSS cancers with *BRAF V600E* mutations have been shown to have an especially poor prognosis.[208] These differences in the prognosis between MSI-H and MSI-L/MSS serrated adenocarcinomas may also have therapeutic implications. While it has been shown that proximal MSI-H CRCs have an inherently favourable prognosis and there is no survival benefit from adjuvant chemotherapy,[209] it is currently not known whether patients with MSI-L/MSS serrated adenocarcinomas would benefit from adjuvant therapies.

Conclusions

Serrated adenocarcinoma represents proof of significant malignant potential of serrated and sessile serrated adenomas. Morphological and genetic characteristics suggest that two parallel serrated pathways can be distinguished: (i) MSI-L/MSS serrated pathway, which has its origin in (traditional) serrated adenomas; and (iii) MSI-H sessile serrated pathway, which has its origin in sessile serrated adenomas and evolves through admixed polyps.

The traditional serrated pathway is characterized by MSI-L or MSS, but it often shows low levels of chromosomal instability and an increased methylation pattern, and is more often localized in the distal colon and rectum. The cancers originating from traditional serrated adenomas usually show a serrated growth pattern and they have a less favourable prognosis than those developing from sessile serrated adenomas.

The 'sessile' serrated pathway usually arises from proximal large hyperplastic polyps or sessile serrated adenomas that may undergo an abrupt adenomatous change, giving them the appearance of an admixed (mixed hyperplastic/adenomatous) polyp, which represents admixed low-grade/high-grade serrated dysplasia. In the sessile serrated pathway, the polyps and carcinomas arising from sessile serrated adenomas represent in many cases the MSI-H phenotype, which develops via *hMLH1* promoter hypermethylation, and the carcinomas arising from sessile serrated adenomas have intrinsically a more favourable prognosis than those arising from traditional serrated adenomas. Thereafter, the biological importance of serrated polyps depends on growth potential and the potential for malignant conversion. The recognition of cases with reasonable potential for recurrences, other metachronous polyps and CRC is essential for the management of these polyps.

While there is consistent evidence that patients with serrated adenomas and admixed polyps require close follow-up, and a sufficient amount of evidence showing that patients with sessile serrated adenomas also need follow-up, the future challenge is to find out which hyperplastic/serrated polyps harbour the risk of progression, in addition to establishing the diagnostic criteria for serrated dysplasia that rank the alterations according to low and high risk of progression.

Serrated adenocarcinoma is a common and distinct subtype of CRC with distinct precursor lesions. It is at least three times more common than HNPCC cancers, and at least six times more common than FAP cancer. Since serrated adenocarcinoma has been associated with both rapid appearance and growth, and as a subset of distal/non-MSI-H serrated adenocarcinomas has been associated with poor prognosis, it is essential that serrated adenocarcinoma be properly recognized. Only recognition of serrated adenocarcinoma as a distinct entity allows it to be further characterized, making it possible to find optimal prevention and treatment modalities for this type of colorectal cancer.

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