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Colorectal Carcinogenesis Based on Molecular Biology of Early Colorectal Cancer, with Special Reference to Nonpolypoid (Superficial) Lesions

Toshiaki Watanabe, M.D., Ph.D., Tetsuichiro Muto, M.D., Ph.D.

Department of Surgical Oncology, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan

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Abstract. The multistep genetic model of colorectal carcinogenesis is based on the concept of the adenoma–carcinoma sequence. The adenoma–carcinoma sequence theory has been generally accepted for polypoid early colorectal cancers (ECCs). On the other hand, an increasing number of nonpolypoid (superficial) ECC have been reported. Nonpolypoid (superficial) ECCs show distinct characteristics histologically and genetically, and some claim these lesions may develop by de novo type carcinogenesis. In fact, clinicopathologic studies have shown that most nonpolypoid (superficial) cancers have no adenomatous lesions in the surrounding area. Genetic analyses have also revealed that nonpolypoid (superficial) ECCs show a pattern of genetic alterations different from that of polypoid ECCs. The K-*ras* mutation rate is lower in nonpolypoid (superficial) ECCs than in polypoid ECCs, but there is no significant difference in the *p53* mutation rate between two types of tumor. During the development of ECCs, the K-*ras* gene seems to determine the macroscopic configuration: whether polypoid or nonpolypoid (superficial). These results suggest that nonpolypoid (superficial) ECCs originate from a pathway different from the conventional genetic pathway that follows the adenoma–carcinoma sequence. However, this does not mean that this new pathway is following de novo type carcinogenesis, because there is a possibility that nonpolypoid (superficial) adenomas, or so-called flat adenomas, develop into nonpolypoid (superficial) ECCs following the adenoma–carcinoma sequence. At the present time, there is still not enough evidence to conclude whether nonpolypoid (superficial) ECC is derived from de novo carcinogenesis or the conventional adenoma–carcinoma sequence. Further analysis, especially concerning *APC* gene mutation in ECCs, is essential to elucidate the carcinogenesis of nonpolypoid (superficial) ECCs.

It has been widely accepted that colorectal cancer develops because of accumulations of genetic mutations within several oncogenes or tumor-suppressor genes. This process of colorectal carcinogenesis is based on the concept of the adenoma–carcinoma sequence and is described by the multistep genetic model [1]. For polypoid early cancers, the adenoma–carcinoma sequence theory has been generally accepted because it is not uncommon for an adenomatous and a carcinomatous component to coexist in a polypoid early cancer [2]. On the other hand, an increasing number of nonpolypoid (superficial) early carcinomas (ECCs) have been reported, particularly in Japan [3–7]. Clinicopathologic studies [5, 8] have shown that there are two groups of colorectal tumor: nonpolypoid (superficial) tumors and polypoid tumors. Nonpolypoid (superficial) tumors are characterized by their macroscopic configuration, as shown in Figure 1.

Nonpolypoid (superficial) ECCs have distinct characteristics histologically and genetically, in contrast to polypoid lesions, which follow the adenoma–carcinoma sequence. Previous studies have demonstrated that these two types of tumor have distinct degrees of invasiveness; nonpolypoid (superficial) tumors tend to reach deeper layers at an earlier stage than polypoid tumors. Fujimori et al. showed that the incidence of high grade dysplasia or cancer was significantly higher in nonpolypoid (superficial) tumors than in polypoid ones and suggested that nonpolypoid (superficial) tumors are more malignant than polypoid tumors [9]. Ikegami also suggested that nonpolypoid (superficial) tumors have characteristics different from those of polypoid tumors, including the ability to invade the submucosal layer rapidly while they are still small [10]. The carcinogenesis of nonpolypoid (superficial) ECCs is still unclear.

It is known that many lesions of the small nonpolypoid (superficial) ECCs are pure cancers without any adenomatous component, so some claim that these lesions develop by de novo carcinogenesis [5, 8]. Recent studies also revealed various genetic changes of nonpolypoid (superficial) ECCs that are different from those of polypoid ECCs. Although there may be another pathway for nonpolypoid (superficial) ECCs that is different from the ordinary adenoma–carcinoma sequence, it does not directly indicate that these lesions arise de novo. There is a possibility that the lesions arise from nonpolypoid (superficial) adenomas, such as flat adenomas, and might form only a subtype of tumors following the adenoma–carcinoma sequence. This article describes the genetic changes of colorectal cancer with special reference to genetic alterations of nonpolypoid (superficial) ECC. The carcinogenesis of nonpolypoid (superficial) ECC is discussed.

Multistep Genetic Model for Colorectal Cancer

Vogelstein et al. reported a multistep genetic model during the adenoma–carcinoma sequence of colorectal carcinogenesis [1, 11]. In this work, the sequential nature of molecular genetic

Correspondence to: T. Watanabe, M.D., Ph.D., e-mail: WATANABE-1SU@h.u-tokyo.ac.jp

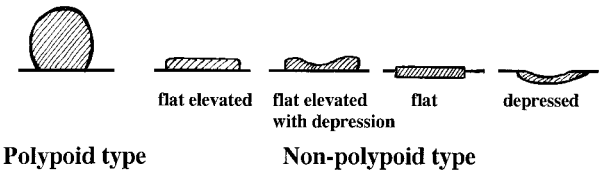

Fig. 1. Macroscopic configuration of colorectal tumors.

changes was proposed. The role of each mutant gene during development and prognosis has been suggested. For an initial step of adenoma formation, alterations take place in the *APC* gene [12, 13]. The *APC* gene has been mapped to chromosome 5q21–22. Mutations in the *APC* gene and loss of heterozygosity (LOH) of chromosome 5q occur at the earliest stage of adenoma formation [14–17] (Table 1). Mutation in the *APC* gene has been detected in about 60% of colorectal tumors regardless of their histopathologic status [15, 18]. LOH of chromosome 5q is considered to occur in one cell of a tumor in which a localized mutation in the *APC* gene is already present and may inactivate the remaining normal copy of the *APC* gene. However, in some cases, LOH of chromosome 5q may be an early event that occurs in cells without a prior *APC* mutation. Powell et al. examined the timing of K-*ras* and *APC* mutation in the adenoma–carcinoma sequence [15]. Among five sporadic adenomas smaller than 1 cm in diameter that were found to have an *APC* mutation, only one lesion had a K-*ras* mutation [15]. Moreover, *APC* mutation has been identified in several adenomas of only 0.5 cm maximum diameter [15]. These results suggested that inactivation of the *APC* gene often precedes K-*ras* mutations during colorectal tumor development.

The second step takes place in the *ras* gene, and it is considered to allow progression from a small adenoma of low malignant potential to a larger, more severely dysplastic one [19, 20]. Although *ras* mutations are thought to arise during early colorectal tumorigenesis [1, 11], it seems to take place after mutation occurs in the *APC* gene. Mutations in one of the *ras* (H-*ras* , K-*ras* , N-*ras*) genes are identified in about 50% of colorectal cancers and in about 50% of colorectal adenomas larger than 1 cm in diameter [1]. In contrast, the frequency of *ras* mutations in adenomas smaller than 1 cm in diameter is approximately 10% [21]. Although mutation of the *ras* gene may not be an initiating event in adenoma formation, adenomas with *ras* mutation may progress more rapidly in growth and the development of dysplasia than adenomas without a *ras* mutation. Most *ras* mutations in colorectal cancer occur at codon 12 of the K-*ras* gene. K-*ras* mutations may arise in one cell of a small preexisting adenoma and contribute directly to its progression to a larger, more dysplastic adenoma.

Alterations of *p53* are thought to contribute to malignant transformation. This takes place after *APC* and K-*ras* mutations [22]. It is suggested that the *p53* gene is mutated in about 75% to 85% of colorectal cancers but infrequently in adenomas [22]. Previous studies demonstrated that tumors containing regions of both adenoma and cancer have suggested that mutation and LOH of the *p53* gene may be directly associated with the progression from adenoma to cancer. In fact, inactivation of the *p53* gene by mutation or LOH (or both) is frequent only in colorectal cancers.

Previous reports have shown LOH at chromosome 17p in more than 70% [23] and point mutation of the remaining allele in about 50% of cases studied [24]. LOH involving chromosome 18q can be detected in approximately 70% of colorectal cancers and in about 50% of advanced adenomas, although infrequently in early-stage adenomas [1]. The *DCC* (deleted in colorectal carcinoma) gene has been identified on chromosome 18q [21], and a correlation between *DCC* and liver metastases has been reported [25, 26]. Also, it has been demonstrated that the prognosis of *DCC*-positive tumors is significantly better than that of *DCC*-negative tumors [27]. Another candidate tumor-suppressor gene (*SMAD4*) was identified on chromosome 18q (18q 21) recently [28]. At the present time, the precise role of these genes has not been clarified. Furthermore, there is still a possibility that other unknown genes are located near these genes on chromosome 18q. New candidate tumor-suppressor genes from this region have yet to be identified.

Genetic Changes of Polypoid and Nonpolypoid (Superficial) ECCs

K-ras *Gene*

Genetic analyses of colorectal adenomas and cancers demonstrated that the frequency of K-*ras* mutation in advanced cancers is lower than that in adenomas with severe atypia [1, 29–31]. According to the multistep genetic model for colorectal carcinogenesis based on the adenoma–carcinoma sequence, genetic changes should be accumulated during the progression from the normal to the malignant tissue. Therefore the decrease in the frequency of K-*ras* mutation from an adenoma with severe atypia to an advanced carcinoma suggests the possibility that some cancers do not arise from adenoma with severe atypia and may develop via a different route, as shown in the original multistep genetic model [32].

On the other hand, studies of nonpolypoid (superficial) colorectal tumors have revealed that alterations of the K-*ras* gene are observed less frequently in nonpolypoid (superficial) tumors than in polypoid lesions [33]. Fujimori et al. examined K-*ras* mutation and the clinicopathologic features of nonpolypoid (superficial) colorectal tumors. They divided colorectal tumors into two groups: polypoid type or superficial type [9]. The K-*ras* mutation rate was lower in the superficial group than in the polypoid group [12% (4/34) vs. 46%(12/26)]. Yagi et al. reported similar results [34]. The frequency of K-*ras* mutation in polypoid and superficial-type tumors (all intramucosal carcinomas) were 44% (10/23) and 17% (4/24), respectively. Both studies showed a lower frequency of K-*ras* mutation in nonpolypoid (superficial) tumors than in polypoid lesions. Our analysis shows compatible results. Yamagata et al. demonstrated that the frequency of K-*ras* mutation was lower in flat adenomas [23% (13/56)] than in polypoid adenomas [67% (54/81)] [35, 36]. Other studies also show the frequency of K-*ras* mutation to be lower in nonpolypoid (superficial) tumors than in polypoid lesions [9, 33–40] (Table 2). Furthermore, several studies examined the K-*ras* mutation rate by dividing nonpolypoid (superficial) tumors into two subtypes, which revealed the difference. Fujimori et al. divided superficial tumors into the following two subtypes: flat elevated type and flat type [9]. Among the 26 flat-type tumors, none showed K-*ras* mutation, whereas 4 of 8 flat elevated lesions showed K-*ras* mutation [0% (0/26) vs. 50% (4/8)] (Table 3). In an analysis by Yagi et al. the K-*ras* mutation rates of superficial elevated and flat-type tumors were 33% (3/9)

Table 1. 5q Loss of heterozygosity and *APC* gene mutation in colorectal tumors.

	LOH of 5q		Mutations of *APC* gene		
Tumor	Vogelstein [16]	Miyaki [14]	Powell [15]	Ichii [17]	Miyaki [14]
Adenoma			63% (10/16)		
Mild or moderate dysplasia	0% (0/34)	0% (0/7)		41% (25/61)	57% (4/7)
Severe dysplasia	9% (5/17)	40% (6/15)		47% (7/15)	60% (9/15)
Cancer			60% (15/25)		
m	29% (4/14)	40% (8/20)			65% (13/20)
sm	36% (21/58)	48% (35/73)			48% (35/73)

m: intramucosal cancer; sm: submucosal cancer; LOH: loss of heterozygosity.

Table 2. Mutation of k-*ras* in polypoid and nonpolypoid tumors.

Study	Histology	Nonpolypoid	Polypoid	*p*
Yukawa [38]	sm Cancer, HGD	0% (0/12)	60% (6/10)	< 0.005
		0% (0/11)	82% (14/17)	< 0.005
Kojima [37]	Tis or T1	14% (3/21)	50% (17/34)	< 0.005
Hasegawa [33]	ECC	23% (7/30)	63% (19/30)	< 0.01
Yagi [34]	m Cancer	17% (4/24)	44% (10/23)	
Minamoto [39]	Adenoma, m/sm cancer	16% (5/31) (adenoma)	—	
		17% (2/12) (cancer)	—	
Fujimori [9]	LGD/HGD	12% (4/34)	46% (12/26)	
Soh [40]	Ad. with SA	0% (0/3) (Ad with SA)	30% (8/27)	
	m/sm cancer	0% (0/5) (M/SM cancer)	29% (10/35)	
Yamagata [36]	Adenoma, m cancer	23% (13/56)	67% (54/81)	

LGD: adenoma with low grade dysplasia; HGD: adenoma with high grade dysplasia; sm cancer: submucosal cancer; m cancer: intramucosal cancer; Ad with SA: adenoma with severe atypia.

Table 3. Mutation of k-*ras* in subtypes of nonpolypoid tumors.

Study	Histology	Nonpolypoid	Polypoid
Fujimori [9]	LGD/HGD	50% (4/8); type IIA**	46% (12/26)*
	Cancer	0% (0/26); type IIB*	
Yagi [34]	m Cancer	33% (3/9); type IIa**	44% (10/23)**
		7% (1/15); type IIb**	
Yamagata [35]	Adenoma	23% (13/56)	67% (54/81)
	m Cancer	38% (9/24) (flat elevated)	—
		9% (2/22) (flat or depressed)	—

Type IIA: flat elevated type; type IIB: flat type; type IIa: flat elevated lesion; type IIb: flat or flat elevated with depression.

*$p < 0.01$.

**$p < 0.02$.

and 7% (1/15), respectively [34]. In Yamagata et al.'s series also, when flat adenomas were divided into two subtypes the K-*ras* mutation rate was lower in flat depressed lesions [38% (9/24)] than in flat elevated lesions [9% (2/22)] [35, 36] (Table 3). The lower frequency of K-*ras* mutation was observed in nonpolypoid (superficial) adenomas and nonpolypoid (superficial) ECCs. K-*ras* is considered to contribute to the progression from a small to a larger adenoma. In general, nonpolypoid (superficial) lesions are small; and therefore these lesions may not require K-*ras* mutation. That the frequency of K-*ras* mutation is low in both nonpolypoid (superficial) adenomas and nonpolypoid (superficial) ECCs, leads to the speculation that nonpolypoid (superficial) adenomas, or so-called flat adenomas, may progress to the nonpolypoid (superficial) ECC and further to advanced cancers. In fact, the high malignancy rate of flat adenomas have been reported previously [41, 42]. If advanced cancers develop by this route from nonpolypoid (superficial) ECCs, they are considered to have the lower frequency of K-*ras* mutation compared to other advanced cancers that have developed from polypoid ECCs by the conventional adenoma–carcinoma sequence. The genetic pathway by which these advanced cancers develop does not include a K-*ras* mutation and therefore is considered to be different from the conventional multistep genetic model.

Based on these results, with respect to precursor lesions, advanced colorectal cancers can be divided into two groups: polypoid ECC-derived or nonpolypoid (superficial) ECC-derived lesions. Cancers which that from polypoid ECCs by the conventional genetic pathway show a high frequency of K-*ras* mutation. In contrast, nonpolypoid (superficial) ECC-derived advanced cancers show a low percentage of K-*ras* mutation. This discrepancy of the K-*ras* mutation rate between two groups of advanced cancers may explain the discrepancy of the mutation rate of the K-*ras* gene between adenomas with severe atypia and advanced cancers, as has been pointed out previously [1, 29–31].

When all cancers develop via the conventional multistep genetic model, the frequency of K-*ras* mutation should not decrease from adenoma with severe dysplasia to advanced cancer. However, a certain percent of advanced cancers seem to develop via the nonpolypoid (superficial) adenoma–nonpolypoid (superficial) ECC–advanced cancer route, which has a low frequency of K-*ras* mutation. Therefore this group of advanced cancers seem to lower the overall frequency of K-*ras* mutation among advanced cancers. Interestingly, in a further analysis of nonpolypoid (superficial) tumors, less frequent alterations of the K-*ras* gene was found in flat-type tumors compared to those in flat elevated-type tumors. Flat elevated-type tumors show a frequency similar to that for polypoid ECCs, whereas flat or depressed-type tumors have a low

Table 4. *APC* gene mutation in nonpolypoid colorectal tumors.

Study	Histology	Nonpolypoid	Polypoid
Yagi [34]	m Cancer	25% (6/24) 44% (4/9); IIa 13% (2/18); IIb*	44% (10/23)*
Aoki [43]	m/sm Cancer	33% (2/6)	—

*$p < 0.04$.

frequency of K-*ras* mutation. This finding suggests that polypoid and flat elevated lesions require K-*ras* mutation, whereas flat or depressed-type tumors do not.

These results suggest that among the nonpolypoid (superficial) ECCs there are two groups of tumors (flat elevated type and flat or depressed type) with respect to the K-*ras* mutation rate. In other words, there is a possibility that flat elevated and flat depressed cancers originate from different pathways. Regardless of whether nonpolypoid (superficial) cancers are derived from the adenoma–carcinoma sequence or de novo carcinogenesis, these results demonstrated that there is a group of cancers, especially among the nonpolypoid (superficial) ECCs, that do not involve K-*ras* gene mutation. These results suggest that different genetic pathways may exist for polypoid and nonpolypoid (superficial) colorectal carcinogenesis.

APC

Because the *APC* gene is considered to be responsible for adenoma formation, an analysis of the gene is essential to elucidate the carcinogenesis of colorectal cancer. To elucidate the nature of the de novo-type carcinogenesis, the most probable candidate of de novo type cancers, which are nonpolypoid (superficial) cancers especially depressed early ECC, must be examined for *APC* mutation. If genetic alterations, including *APC* mutation, in de novo-type cancers are different from those proposed in the multistep genetic model following the adenoma–carcinoma sequence, there may be two distinct genetic pathways for the development of colorectal cancers. If the same genes are involved in both types, the order in which the genetic alterations occur or the time period during which they accumulate may determine which of two clinicopathologic types will ensue.

To address these questions, Aoki et al. searched for genetic alterations in small and flat de novo-type colorectal cancers from six nonpolyposis tumor patients [43]. Two patients (33%) showed APC mutation (Table 4). Both patients were predicted to have truncation of the *APC* product, which is often observed in mutations of sporadic colorectal cancers. Yagi et al. examined *APC* gene mutation in 47 ECCs (23 polypoid and 24 non-polypoid, superficial ECCs) [34] (Table 4). *APC* mutations were observed in 44% (10/23) of the polypoid ECCs and in 25% (6/24) of the nonpolypoid (superficial) ECCs. The polypoid ECCs showed a higher percentage of *APC* mutation than did the nonpolypoid (superficial) ECCs.

The authors then divided nonpolypoid (superficial) ECC into two subgroups: a slightly elevated group and a flat or depressed group. When *APC* mutation was compared between these two subgroups, the slightly elevated tumor group showed a higher percentage of *APC* mutation than the flat or depressed tumor group: 45% (4/9) versus 13% (2/15), respectively. In their analysis, polypoid ECCs and slightly elevated ECCs had similar frequencies of *APC* mutation, whereas the depressed-type ECC had a lower percentage. Because *APC* mutation was frequent in both polypoid and slightly elevated ECCs, they suggested that these lesions constitute a group of colorectal cancers that follow the adenoma–carcinoma sequence. However, the other nonpolypoid (superficial) ECCs, which are classified as the flat or depressed group, rarely showed *APC* mutation. Therefore, for these lesions they suggested that a distinct pathway is required for colorectal carcinogenesis to develop, and possibly other gene mutations are involved. However Yagi et al.'s ECC series included only intramucosal carcinomas and not submucosal cancers [34].

Differentiation between cancers of the de novo-type carcinogenesis and the adenoma–carcinoma sequence is difficult because nonpolypoid (superficial) cancers may arise from foci of dysplasia within the mucosa just as polypoid cancers arise from dysplasia within polypoid adenomas. Further analysis of the *APC* mutation in a larger number of nonpolypoid (superficial) ECCs, not only intramucosal carcinomas but also submucosal cancers, is needed elucidate the de novo-type carcinogenesis genetically.

p53 *Gene*

Yamamura et al. examined *p53* mutations in polypoid and nonpolypoid (superficial) colorectal tumors [44]. They found no significant difference in the frequency of *p53* mutations between polypoid and nonpolypoid (superficial) ECCs: 40% (4/10) and 33% (2/6), respectively [44]. Thus they suggested that *p53* mutation did not appear to play a role in determining the growth pattern of ECC, whether polypoid or non-polypoid (superficial). Also, they revealed that the mutation rate of *p53* is affected by the histologic features. The *p53* gene mutated in 16% of high grade dysplasias (3/19 lesions) and 38% of ECCs (6/16 lesions). No mutation was detected in 14 adenomas with low grade dysplasia. Therefore they suggested that *p53* gene mutation is involved in the conversion from adenoma to cancer in nonpolypoid (superficial) and polypoid colorectal tumors. Aoki et al. examined *p53* mutation in six small flat ECCs (five lesions with intramucosal carcinoma and one carcinoma with submucous invasion); they found *p53* mutation was present in 67% (4/6) of lesions [43].

These studies examined *p53* mutations by sequencing. Previous immunohistochemical analyses have also compared overexpression of *p53* in polypoid and nonpolypoid (superficial) ECCs (Table 5). Yukawa et al. examined the *p53* overexpression rate in ECCs immunohistochemically [38]. They divided ECCs into polypoid or flat type-tumors, the flat type being a nonpolypoid (superficial) type in the present study. Among 12 flat lesions, 6 (50%) were positive for *p53* staining (4 among 10 polypoid tumors, or 40%). No significant difference was seen in the *p53* overexpression rate between polypoid and flat tumors. Another immunohistochemical analysis also demonstrated the 73% of *p53* overexpression in nonpolypoid (superficial) tumors [63% (15/24)] among intramucosal carcinomas and 88% (14/16) in ECCs [45]. These results demonstrate that there is no significant difference in the mutation rate of *p53* for polypoid and nonpolypoid (superficial) tumors.

The *p53* mutations are considered to be important late events in colorectal carcinogenesis [22]. They do not seem to contribute to

Table 5. Alterations of the *p53* gene in polypoid and nonpolypoid colorectal tumors.

Configuration	Wada [45]	Yukawa [38]	Yamamura [44]	Aoki [43]
Nonpolyoid				
sm Cancer		63% (15/24)	50% (6/12)	40% (4/10)
100% (1/1) Adenoma				
HGD	88% (14/16)*	9% (1/11)	29% (2/7)	60% (3/5)*
LGD		0% (1/20)	0% (0/5)	
Polypoid				
sm Cancer Adenoma	—	40% (4/10)	33% (2/6)	—
HGD	—	12% (2/17)	8% (1/12)	—
LGD	—	0% (0/28)	0% (0/9)	—
Method	Immunohistochemistry	Immunohistochemistry	PCR-TGGE sequence	Sequence

PCR-TGGE: polymerase chain reaction.
*Intramucosal carcinoma.

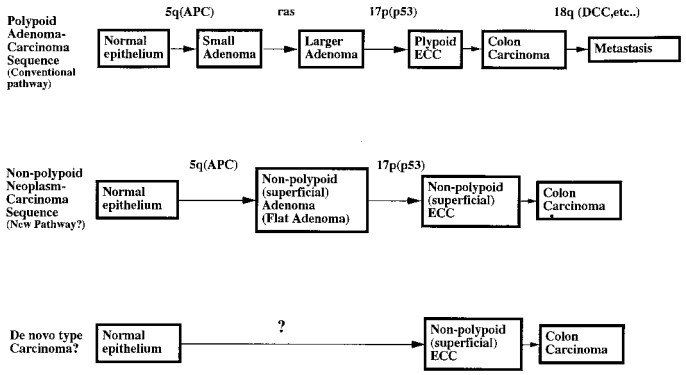

Fig. 2. Genetic model for colorectal tumorigenesis. APC: the *APC* (adenomatous polyposis coli) gene; DCC: the *DCC* (deleted in colorectal cancer) gene; ECC: early colorectal cancer.

the formation of the various macroscopic types of ECC, whether polypoid or nonpolypoid (superficial).

Genetic Pathway for ECC

Molecular analyses have revealed several characteristics of nonpolypoid (superficial) ECC. The most striking difference between polypoid and nonpolypoid (superficial) ECCs was the mutation rate of the K-*ras* gene. Both nonpolypoid (superficial) adenomas and ECCs had a lower frequency of K-*ras* mutation than polypoid lesions. As for the *p53* gene, there seems to be no significant difference between polypoid and nonpolypoid (superficial) ECCs.

The mutation rate of the *APC* gene has been reported to be low in nonpolypoid (superficial) lesions. However, most of the previous studies examining *APC* gene alterations have dealt with intramucosal carcinomas and not ECC with submucosal invasion. Therefore, at the present time it is difficult to evaluate the true frequency of *APC* gene mutation in nonpolypoid (superficial) ECCs. Further studies are needed to elucidate the true nature of alterations of the *APC* gene in nonpolypoid (superficial) ECC.

Less frequent alterations of the K-*ras* gene in nonpolypoid (superficial) ECC compared with polypoid ECC suggests that nonpolypoid (superficial) ECC may originate from a pathway different from the conventional genetic pathway following the adenoma–carcinoma sequence (Fig. 2). According to this model, the K-*ras* gene is considered to be essential for determining the macroscopic configuration of the ECC whether polypoid or nonpolypoid (superficial). When the K-*ras* gene has mutated, tumors grow large and become polypoid; when K-*ras* has not mutated, tumors progress to nonpolypoid (superficial) ECCs. Although this new pathway is distinct from the conventional genetic route, it still follows the adenoma–carcinoma sequence because nonpolypoid (superficial)-type adenomas are considered to be precursors of nonpolypoid (superficial) ECCs. In contrast to this new possible route, some claim that there is a possibility that nonpolypoid (superficial) cancers derive from de novo-type carcinogenesis. In fact, clinicopathologic studies have shown that most of the nonpolypoid (superficial) cancers have no adenomatous lesions in the surrounding area [10]. There is still not enough evidence to conclude whether nonpolypoid (superficial) cancer is derived from de novo-type carcinogenesis or a flat adenoma via the adenoma–carcinoma sequence. Interestingly, some studies have revealed that there are two subtypes within nonpolypoid (superficial) ECC with regard to the K-*ras* mutation rate: flat elevated type and the flat type (including depressed lesions or flat elevated lesions with depression). Flat elevated tumors have K-*ras* mutation at a frequency similar to that of polypoid lesions, whereas flat tumors have a low percentage of K-*ras* mutation [9, 34–36]. One study demonstrated that flat tumors show a lower percentage of *APC* gene mutation as well.

These results may suggest the possibility that nonpolypoid (superficial) ECC have two routes of carcinogenesis. Among flat elevated tumors the flat adenomas may progress to nonpolypoid (superficial) ECC following the adenoma–carcinoma sequence, whereas among flat tumors the nonpolypoid (superficial) ECCs may develop directly from the normal mucosa via the de novo-type carcinogenesis (Fig. 3). Further analysis, especially of *APC* gene mutation in nonpolypoid (superficial) ECC, is essential to elucidate the carcinogenesis of nonpolypoid (superficial) ECC.

Conclusions

Genetic analyses have revealed that nonpolypoid (superficial) ECCs show a pattern of genetic alterations different from that of polypoid ECCs. Mutation of the *p53* gene shows no significant difference between two groups, but the K-*ras* mutation rate is lower in nonpolypoid (superficial) ECCs. These results suggest that different genetic pathways for tumor progression may exist for polypoid and nonpolypoid (superficial) ECCs. Whether nonpolypoid (superficial) ECC is derived from de novo-type carcino-

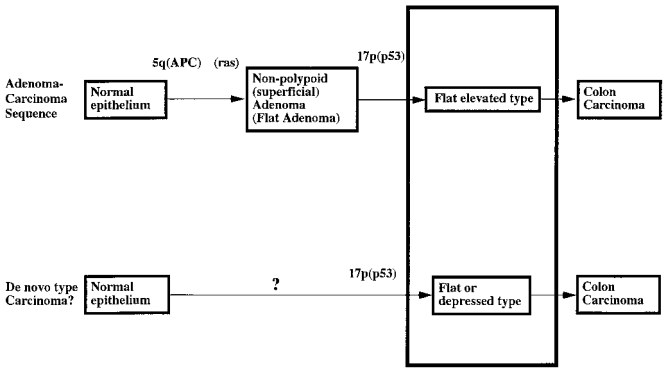

Fig. 3. Genetic model for nonpolypoid (superficial) ECC.

genesis, most nonpolypoid (superficial) ECCs have been shown not to harbor K-*ras* mutation. Further studies, especially those revealing *APC* gene alterations, are essential to elucidate the carcinogenesis of nonpolypoid (superficial) ECC.

Résumé

Le modèle génétique multi-étape de la carcinogenèse colorectale est basé sur le concept de la séquence adénome/cancer. Pour les cancers polypoïdes «au début» (CPD), la théorie de la séquence adénome-cancer est généralement acceptée. En revanche, on a rapporté un nombre croissant de cancers «au début» non-polypoïdes («superficiels»). Ces tumeurs ont des caractéristiques histologiques et génétiques bien distincts et certains pensent que ces lésions pourraient se développer à partir d'une carcinogenèse «de novo». En vérité, les études clinicopathologiques ont montré que la plupart des cancers non-polypoïdes (superficiels) ne sont pas accompagnés de lésions adénomateuses dans les alentours. L'analyse génétique a également révélé que les cancers au début non-polypoïdes (superficiels) avaient des altérations génétiques différentes par rapport aux cancers polypoïdes: le taux de mutation K-ras était plus bas dans les cancers au début non-polypoïdes (superficiel) que dans les cancers au début polypoïdes, alors qu'il n'y avait aucune différence significative dans le taux de mutation p53 entre les deux types de tumeurs. Dans le développement des tumeurs au début, le gène K-ras semble déterminer la configuration macroscopique polypoïde ou non-polypoïde. Ces résultats suggèrent que les cancers colorectaux non-polypoïdes (superficiels) puisse prendre naissance d'une séquence différente de la séquence adénome/cancer. Cependant, ceci n'implique pas forcément que cette nouvelle séquence suit la carcinogenèse de novo, car il est possible que les adénomes non-polypoïdes (superficiels), appelés aussi les adénomes plats, évoluent vers les cancers non-polypoïdes, suivant la séquence classique. A présent, il n'y a pas encore suffisamment d'évidence pour conclure si le cancer au début non-polypoïde se développe selon une carcinogenèse de type de novo ou selon la séquence conventionnelle adénome-carcinome. Une analyse supplémentaire, surtout en ce qui concerne la mutation du gène APC dans le cancer au début, est nécessaire pour élucider la carcinogenèse des cancers colorectaux non-polypoïdes (superficiels).

Resumen

El patrón genético en la carcinogénesis del cáncer colorrectal se basa en el concepto secuencial, bien conocido, de la transformación del adenoma en cáncer. Habitualmente, se acepta esta teoría para explicar la génesis de los cánceres precoces polipoideos (ECC). Sin embargo, cada vez son más frecuentes los cánceres no-polipoideos (superficiales). Estos ECC presentan unas características tanto histológicas como genéticas distintas, por lo que algunos autores creen, que estas lesiones neoplásicas se originan "de novo". En efecto, diversos estudios clínico-patológicos han demostrado la inexistencia, en la mayoría de los cánceres superficiales (no-polipoideos), de lesiones adenomatosas, ausentes incluso en las áreas circundantes. Análisis genéticos demostraron, un patrón diferente de alteraciones genéticas entre los ECC polipoideos y no-polipoideos (superficiales). La tasa de mutación K-ras es menor en los ECC superficiales que en los polipoideos, no observándose entre ambas neoplasias, diferencias significativas por lo que a la tasa de mutación del p53 se refiere. En el desarrollo de los ECC, el gen K-ras parece determinar la configuración macroscópica, es decir, si se desarrollarán tumores polipoideos o superficiales. Estos hallazgos sugieren, que la carcinogénesis de los ECC superficiales difiere de la secuencia convencional: adenoma-carcinoma. Sin embargo, este desarrollo diferente no implica "per se" una carcinogénesis "de novo", pues existe la posibilidad de que adenomas planos se transformen en ECC superficiales, siguiendo la secuencia convencional. En la actualidad, no existen datos suficientes que demuestren que los ECC no-polipoideos (superficiales) se originen como consecuencia de una carcinogénesis "de novo" en vez, de seguir la secuencia convencional adenoma-carcinoma. Análisis complementarios, especialmente por lo que se refiere a la mutación del gen APC en los ECC, son imprescindibles para aclarar la carcinogénesis de los ECC no-polipoideos (superficiales).

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