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TOPIC HIGHLIGHT

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Early-onset colorectal cancer: A separate subset of colorectal cancer

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Abstract

Colorectal cancer (CRC) has a great impact on the world population. With increasing frequency, CRC is described according to the presenting phenotype, based on its molecular characteristics. Classification of CRC tumors according to their genetic and/or epigenetic alterations is not only important for establishing the molecular bases of the disease, but also for predicting patient outcomes and developing more individualized treatments. Early-onset CRC is a heterogeneous disease, with a strong familial component, although the disease is sporadic in an important proportion of cases. Different molecular alterations appear to contribute to the apparent heterogeneity of the early-onset population and subgroups can be distinguished with distinct histopathologic and familial characteristics. Moreover, compared with late-onset CRC, there are characteristics that suggest that early-onset CRC may have a different molecular basis. The purpose of this review was to analyze the current state of knowledge about early-onset CRC with respect to clinicopathologic, familial and molecular features. Together, these features make it increasingly clear that this subset of CRC may be a separate disease, although it has much in common with late-onset CRC.

Key words: Chromosomal instability; CpG island methylator phenotype; Early-onset colorectal cancer; Lynch syndrome; Microsatellite instability

Core tip: Early-onset colorectal cancer is a heterogeneous disease with various molecular alterations, in which different subgroups with different histopathologic and familial characteristics can be distinguished. Classification of colorectal cancer tumors according to their genetic alterations is important for establishing the molecular bases of the disease, as well as for predicting patient outcomes and developing more individualized treatments.

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INTRODUCTION

Colorectal cancer (CRC) has a great impact on the world population. The estimated incidence is 1.2 million new cases per year. It is the third most common malignancy and the second leading cause of death in developed

Table 1 Main pathways involved in the onset and development of colorectal cancer

	Chromosomal instability or "suppressor" pathway	Microsatellite instability or "mutator" pathway	CpG island methylator phenotype or "serrated" pathway
Percentage of CRC	80%-85%	10%-15%	40%
Clinical characteristics	Predominant location of tumor in the distal colon	Predominant location of tumor in the right colon Better prognosis	Predominant location of tumor in the right colon Female sex
Histopathologic characteristics	No lymphocytic reactions No mucinous features Good differentiation	Lymphocytic reactions Mucinous features Signet ring cells Low-grade tumor differentiation	Low-grade tumor differentiation
Molecular characteristics	Aneuploidy, polyploidy, loss of heterozygosity	Diploidy, MSI	Methylation of CpG islands
Main genes involved	*APC, P53, KRAS, C-MYC, DCC/SMAD4, TGFBR, PIK3CA*	*MLH1, MSH2, MSH6, PMS2, TGF-βRII, IGFIIR, MSH3* and *BAX*	*BRAF, MSI*
Hereditary syndromes	Familial adenomatous polyposis	Lynch syndrome	

CRC: Colorectal cancer; MSI: Microsatellite instability.

countries[1-3]. In Spain, CRC incidence projections for the population in 2015 are about 30000 people (17000 men and 13000 women)[4]. Early-onset CRC accounts for 2%-8% of all CRCs. Furthermore, its incidence in the United States increased by 1.5% per year in men and by 1.6% in women between 1992 and 2005. The growing frequency of CRC in young adults contrasts with the progressive decline of CRC among older people. This underscores the importance of early evaluation in cases of young adults with compatible symptoms[5,6].

The classical model of colorectal carcinogenesis for the adenoma-carcinoma sequence has been evolving since its original formulation[7] thanks to advances in our understanding of the molecular mechanisms involved. CRC is, nowadays, described with increasing frequency, according to the molecular characteristic of the presenting phenotype; thus, the molecular classification of CRC is gaining importance[8]. Particularly, studies analyzing the possible basis of early-onset CRC have evolved: in early studies, the principle prevailed that early-onset is an indicator of a hereditary component[9,10], whereas currently, the concept prevails that it is a heterogeneous disease, which includes cases with a strong familial component as well as cases of sporadic disease. Different molecular alterations appear to contribute to the apparent heterogeneity of early-onset CRC and subgroups can be distinguished with distinct histopathologic and familial characteristics[11].

The aim of this review was to analyze the current knowledge of the molecular basis of early-onset CRC, and its relationship with the particular clinicopathologic and familial features of this subset.

CARCINOGENETIC PATHWAYS OF CRC

To date, three main pathways involved in the formation and development of CRC have been identified: the chromosomal instability (CIN) or suppressor pathway; the microsatellite instability (MSI) or mutator pathway; and the CpG island methylator phenotype (CIMP) or serrated pathway (Table 1). These three pathways differ from the clinicopathologic, familial and prognostic points of view. While they are overlapping, they are the dominant mechanisms that determine the final phenotype[12].

Most (80%-85%) sporadic CRCs involve the CIN pathway, which is characterized by alterations in the number and structure of chromosomes and frequent loss of heterozygosity. Cases of familial adenomatous polyposis with germline mutations in *APC* also show CIN; these tumors are also referred to as having microsatellite stability (MSS). Genetic changes include the activation of proto-oncogenes such as *KRAS* and *C-MYC* and inactivation of the tumor suppressor genes, *APC*, and *p53*, and loss of heterozygosity for the long arm of chromosome 18. Recently, mutations in the genes *TGFBR* and *PIK3CA* have been described, which are involved in the adenoma-carcinoma sequence[3,13-16].

MSI tumors, whose carcinogenetic pathway is also known as the "Mutator Phenotype pathway", represent 10%-15% of all CRCs. MSI is due to an inability of the DNA nucleotide mismatch repair (MMR) system to correct errors that often occur during DNA replication, which is controlled by several genes (including *MLH1*, *MSH2*, *MSH6* and *PMS2*) and is characterized by the accumulation of single nucleotide mutations and alterations in the lengths of repetitive microsatellite nucleotide sequences[15,17,18]. Apart from genes related with the DNA nucleotide MMR system, other tumor suppressor genes such as *TGF-βRII*, *IGFIIR*, *MSH3* and *BAX* are involved[19]. MSI tumors are present in two CRC forms: hereditary forms such as lynch syndrome (LS), the molecular basis of which is a germline mutation in an MMR gene; and sporadic cases, in which MSI is due to hypermethylation of *MLH1*[20]. MSI tumors are characterized by a more frequent location in the right colon, increased mucin production, the presence of signet ring cells, and low-grade tumor differentiation[18].

Analysis of the methylation of CpG islands as a mechanism of silencing genes in colon tumors has re-

Table 2 Main features of molecular classification

Category	CRC	Characteristics		
		Molecular	Histopathologic	Clinical
MSI/CIMP-high	10%	MLH1 methylation BRAF mutations	Poor differentation Lymphocytic reaction Mucinous/signet ring cells	Predominant location of tumor in right colon Elderly females Sporadic MSI
MSI/CIMP-low/0	5%	MMR Negative for BRAF mutations	Lymphocytic reaction Mucinous features No signet ring cells Good or moderate differentation	LS
MSS/CIMP-high	5%-10%	BRAF mutations and methylation of multiple other genes	Poor differentation Signet ring cell	Predominant location of tumor in right colon Elderly females
MSS/CIMP-low/0	75%-80%	CIN KRAS mutations	Well differentiated Heterogeneous	Predominant location of tumor in distal colon Male sex

CIMP: CpG island methylator phenotype; CIN: Chromosomal instability; CRC: Colorectal cancer; LS: Lynch syndrome; MMR: Mismatch repair; MSI: Microsatellite instability; MSS: Microsatellite stability

sulted in the identification of a third major pathway (CIMP), which accounts for almost 40% of CRCs[21-23]. This carcinogenetic mechanism is also known as the "serrated pathway", because CRCs of this subset often arise from a serrated precursor lesion. CIMP-high tumors have a distinct clinical, pathologic, and molecular profile, such as association with proximal location in the colon, female sex, and poor differentiation. From the molecular point of view, they show a higher frequency of *BRAF* mutations, MSI and, albeit less often, *P53* mutations[13,24,25].

Until recently, only MSI tumors were thought to be CIN^-, and CIN^+ tumors were thought to have an intact MMR system and to show MSS. However, several studies have demonstrated that up to 50% of MSS tumors are CIN^- [also called microsatellite and chromosome-stable (MACS) tumors], and a significant, but smaller, portion of MSI colorectal tumors are CIN^+. MACS tumors are being characterized and some of their features are a preference for the distal colon and rectum, histologic features associated with poor prognosis, and more frequent identification in younger cases[26,27].

MOLECULAR CLASSIFICATION

As mentioned previously, carcinogenesis pathways are not mutually exclusive. Classification of CRC tumors according to the genetic and/or epigenetic alterations observed is important to establish the molecular bases of the disease, as well as to predict patient outcomes and to develop more individualized treatments. For this reason, a molecular classification has been gaining strength that is based on the three global cellular events (CIN, MSI and CIMP) and reflects underlying mechanisms of carcinogenesis; it correlates with some phenotypic characteristics, as described in our previously published study[28]. Globally, sporadic CRC should be classified into four major subtypes: two MSI statuses (MSI-H *vs* MSI-L/MSS) times two CIMP statuses (CIMP-H *vs*. CIMP-low/0), with distinct molecular correlates (*BRAF*, *KRAS*) and pathologic features[8]. In Table 2, the main features are summarized that define each category[8,15].

EARLY-ONSET CRC

Clinicopathologic characteristics

Currently, there are some controversial aspects to the natural history and prognosis of early-onset CRC, and there are also some clinical and pathologic differences when comparing with CRC in the elderly[9,29].

Mucinous and signet ring cell tumors account for 10%-15% and 1% of all CRCs, respectively. Several reports indicate that early-onset CRC is clinically and pathologically characterized by a predominance of low-grade tumor differentiation, mucinous tumors, and a higher percentage of signet ring cells; these features are shared with hereditary CRC forms[9,30,31]. In addition, some studies have found a relationship between mucinous CRC and poor prognosis[32-34]. Early-onset CRC is associated with a higher percentage of synchronous and/or metachronous tumors, as well as with an increased development of polyps during follow-up[10,35]. Studies addressing the early-onset group within CRC showed important variations concerning tumor location. Some of them found a striking predilection for the distal colon, particularly the sigmoid colon and rectum[33,36]; furthermore, recent studies show an increased incidence of rectal cancer in adults younger than 50 years[34,37]. However, in other series the highest percentage of CRC was seen in the right colon, and a greater proportion of patients had a family history of CRC, suggesting that CRC in the proximal colon in young patients may reflect a genetic predisposition[30,31].

Generally, early-onset CRC is diagnosed at advanced stages. One reason that could explain this is the absence of screening programs for CRC in patients under 50 years, except in cases of family or personal history of cancer[38]. On the other hand, the aggressive histopathologic characteristics of the tumor and a possible genetic basis may predispose to accelerated development of this tumor in young patients[39,40]. Regarding reports in the literature, there are studies showing that CRC in young patients has a poor outcome[32,39]. However, other series found equivalent survival rates in younger patients with CRC compared with older patients, despite presenting a

Table 3 Proportion of microsatellite instability in early-onset colorectal cancers series and their age of onset

Study	Age of CRC onset, yr	Population	MSI, *n* (%)
Losi *et al*[9]	≤ 45	Unselected CRC surgical patients	71 (19.7)
Liang *et al*[10]	≤ 40	Unselected CRC surgical patients	138 (40.5)
Perea *et al*[11]	≤ 45	Unselected CRC surgical patients	88 (13.6)
Jasperson *et al*[50]	< 36	Hereditary cancer registries	96 (29.1)
Durno *et al*[51]	< 25	Familial cancer registry	16 (72.7)
Farrington *et al*[52]	< 30	Cancer registries	50 (47.5)
Antelo *et al*[66]	< 50	Cancer registry	118 (22.9)

CRC: Colorectal cancer; MSI: Microsatellite instability.

more advanced stage of disease[41]. These discrepancies may be explained by the inclusion of hereditary CRC, particularly LS, which has a better survival rate than sporadic CRC in young patients[42]. The review by Chang *et al*[33] shows that early-onset CRC, despite having histologic features that are related to worse prognosis, presents overall and disease-free survival rates similar to those seen in patients over 40 years, but in contrast, also has a higher incidence of recurrence and development of distant metastases. These results agree with those published by Yeo *et al*[43], with a median survival at five years in their series of 59.4% in patients under 40 years, and of 61.1% in patients older than 40, while the rate of metastases and locoregional recurrence was greater in the young group.

Familial characteristics

Early-onset CRC includes cases with strong familial history and cases with sporadic disease. It is well known that in this population identification of cases of LS is more likely, even more so when the age of onset is younger[11,44,45]. Apart from that, the familial component within this age of onset group is so important, that when we leave aside LS, there is still a clear familial component in this population: Compared to elderly MSS CRC, early-onset CRCs with the same component show more familial aggregation and Lynch-type tumors, a fact that may be related to new hereditary CRC syndromes, such as Familial CRC syndrome type X[46-49].

Molecular characteristics

From a molecular point of view, two main aspects have been addressed among the subset of early-onset CRCs: on the one hand, the analysis of proportions of cases with MSI and the necessary relationship with LS, and on the other hand cases with molecular alterations that relate to carcinogenesis pathways associated with CIN.

MSI analysis: LS and sporadic cases

Early-onset of cancer is a marker of a potentially hereditary component, with LS being the most frequent hereditary form of CRC. Nevertheless, the proportion of MSI tumors found within early-onset CRC varies from 19.7% to 41.0%, depending on the age of onset. As shown in Table 3, MSI frequency is inversely proportional to the age at diagnosis and directly proportional to the LS component of the series[9-11,48,50-52]. In our recent study, twelve out of 82 (15%) early-onset cases were defined as MSI[28]. In all cases, MSI correlated with lack of detectable expression of any of the MMR proteins in immunohistochemical analysis, and 83% of them were explained by a mutation in one of the MMR genes. Moreover, we later confirmed that MSI tumors in the younger population are mostly related to LS and rarely due to somatic inactivation of *MLH1*[28], showing that the criterion of early age of onset, together with other clinicopathologic and familial features, is helpful in identifying LS cases[11]. In contrast, diagnosis of LS in early-onset CRC is highly unlikely in patients with certain combinations of clinical and familial features: *e.g.*, left-sided CRC and absence of family history[49].

As expected, early-onset MSI CRC shows some clinical and pathologic features similar to those described for LS: more frequent right-sided colon tumors, frequently poorly differentiated tumors showing mucin production and signet ring cells, and a more frequent development of synchronous and metachronous tumors[42,53,54]. Prognosis for MSI tumors is better than for MSS tumors, and as MSI tumors are hypermutated, mutation rate may be a better prognostic indicator for this age of onset[27,42,55,56].

CIN analysis

The majority of early-onset CRC are MSS tumors, and there are few studies that evaluate the clinicopathologic features of this subset of CRC within the early-onset population[46,57,58]. MSS tumors are characterized by a later age of onset, lower prevalence in the right colon, and fewer synchronous and metachronous tumors; they also tend to be diagnosed at later stages and more frequently show adverse histologic features[33]. Compared with late-onset cases showing MSS, early-onset MSS tumors are remarkably different, as highlighted by the important rate of left colon location, low frequency of other primary neoplasms, and the presence of an important familial component[24,28,46].

We previously pointed out the importance of age of onset to make an appropriate approach to the molecular classification of CRC, given the possible different molecular bases of early-onset CRC compared with elderly CRC[28]. Apart from some preliminarily defined molecular markers (modified expression of the *APC*, *B-catenin* and *P53* genes), new findings have been reported concerning MSS early-onset CRC[59]. The main emerging key aspects

are: (1) analysis of MACS tumors: these tumors, particularly when they are located in rectum, appear to have longer telomeres than those of MSS CIN rectal cancers and use alternative lengthening of telomeres rather than activation of telomerase[60]; and (2) the use of high resolution tumor genome copy number variations in order to identify differences in the tumor genomes between these groups and to pinpoint potential susceptibility loci. Comparing two MSS CRC groups with different ages of onset, Berg *et al*[61] identified ten genomic loci, containing more than 500 protein-coding genes, as more often altered in tumors from early-onset *vs* late-onset CRC. In addition, integration of genome and transcriptome data identified seven novel candidate genes with the potential to identify an increased risk for CRC[61].

CIMP analysis

CIMP has been rarely evaluated within early-onset CRC. Previous large series, without using age of onset as a differential criterion, showed that LS cases were mainly included in the CIMP-low group, while sporadic MSI cases were more likely to be CIMP-high, with high rates of *BRAF* mutations[8]. Nevertheless, these features are observed within the late-onset CRC group, whereas in early-onset CRC, LS primarily has a higher percentage within the CIMP-high group. This could be the consequence, among others, of a low number of *BRAF* mutations and hypermethylation of the *MLH1* promoter in early-onset CRC[28,36,57,58]. It is known that the difference between CIMP-low and CIMP-0 is unclear when considering CRC in general. Within the early-onset population, a number of differences with the elderly group draw attention: a progressive disappearance of right colon tumors, a higher rate of CIMP-low cases, and an important familial component: LS-related tumors, but also cancer history, are observed in cases of CIMP-low or CIMP-0, with an important number of LS-related neoplasias[28].

MACS

Some tumors with MSS have recently been identified that, contrary to expectations, do not have CIN. Furthermore, they do not strictly fit with tumors involving the serrated pathway. This subset of CRC, defined as MACS, is identified most frequently in younger cases. It is also more frequently observed in the distal colon and rectum, has histologic features associated with poor prognosis and some familial aggregation for LS neoplasms[47]. MACS tumors also present metastases at diagnosis[46,62]. Banerjea *et al*[62] showed that patients with MACS tumors had early disease recurrence and lower survival than patients with MSI or CIN tumors. This important circumstance is due to a diminished or inhibited immune response to MACS tumors in comparison with other CRC phenotypes[62]. Regarding family characteristics, some published studies conclude that MACS may be related to familial CRC syndromes, based on an observed increased frequency in young patients with a family history. However, other studies illustrate that MSS and CIN CRCs are not necessarily related to hereditary tumors[47,63]. Little is known about MACS from a molecular point of view, but it seems that these tumors have a different methylation profile that involves genes not known to be involved in global CCR. Several studies have found that MACS tumors are associated with CIMP-low, that they rarely have *BRAF* gene mutations and absent *MLH1* expression, and they seem to have a different pattern of hypomethylation when compared to MSI and CIN CRC. This has raised the possibility that LINE 1 hypomethylation may be related to MACS[64-66]. Recently, LINE-1 hypomethylation has been shown to be a feature of young-age of onset CRC, and it is also associated with family history of CRC. According to the molecular classification of CRC, CIMP-high and MSI-high are inversely associated, while MSS tumors are correlated with LINE-1 hypomethylation, and genomic hypomethylation may represent different pathways to CRC[67].

Molecular classification

The first classification of CRC to correlate the main molecular carcinogenetic pathways was proposed by Jass[68], and was later modified by Ogino and Goel[8]. Based on MSI and CIMP status, CRC should be classified into four major subsets, with some features particular for each one, as has been described previously.

Perea *et al*[28] carried out a comparative analysis of MSI status and CIMP in two series of early-onset and late-onset CRCs, in order to evaluate molecular classification according to age of onset. It was the first study that characterized early-onset CRC based on its molecular classification, and the main differences found, compared with the features of previously described global CRC, were: (1) early-onset MSI/CIMP-high tumors were Lynch tumors, whereas elderly MSI/CIMP-high tumors were associated with *BRAF* mutations; (2) half of early-onset MSI/CIMP-low/0 cases were Lynch tumors with a mucinous component and were left-sided. According to these results, the early-onset criterion would make a change in the MSI groups of Ogino and Goel's molecular classification[8], particularly in MSI/CIMP-high tumors, because they would contain the main proportion of LS within early-onset MSI CRC[28,36,57]; (3) the MSS/CIMP-high category had more similarities, although there was a remarkably important familial component in the early-onset subset of tumors, mainly regarding LS-related neoplasm aggregation; and (4) the most common group within the early-onset population was formed by MSS/CIMP-low/0 tumors, showing a preference for the distal colon and containing an important familial cancer component.

Location characteristics

Several studies suggest that tumor location is one of the most influential factors of CRC morphology. When comparing the characteristics of CRCs according to their location, differences are observed in terms of epidemiologic, clinicopathologic, familial, genetic and risk factors[69-73]. Increasingly, it is suggested that these differences between

tumors of the right and the left side of the colon and the rectum may be due to differences in embryologic origin, or to different physiologic, biologic and gene expression properties. This would condition different carcinogenetic pathways depending on the location in one or another region of the colon[71,72,74].

To our knowledge, there are no published studies to date that examine the phenotype of CRC in young adults according to the location of the tumor. Globally, cancer of the right colon is frequently observed in the elderly and in women, whereas cancer of the left colon predominates in young people and in men[69,75-79]. Indeed, several studies show an increased incidence of rectal cancer in patients younger than 50 years[34,37]. Regarding histopathologic features, tumors in the right colon have been associated with a low degree of differentiation and a higher frequency of signet ring cells and mucin production when compared to left and rectum tumors. These characteristics are also described for early-onset CRC[66,73]. Regarding family characteristics, neoplasms located in the right colon are more frequently associated with LS[48,50,80]. However, some studies draw attention to the high percentage of cases with a family history of tumors located in the rectum and left colon within early-onset CRC[28]. These cases could be related, as mentioned previously, to new hereditary syndromes whose molecular bases and phenotypic characteristics are not yet known, such as Familial CRC syndrome type X[46-49].

Finally, knowledge of the molecular characteristics of early-onset tumors at different locations in the colon is limited. Regardless of the age of onset, Bufill[70] suggested that proximal colon cancers and distal CRCs have arisen through different genetic pathways. Subsequently, different studies described the preference of CIMP and MSI in proximal colon cancer and of CIN and *P53* mutation in distal and rectal cancer[56,81,82]. In our recent study that analyzed 88 young patients with CRC, we observed a gradual decrease in the frequencies of CIMP and MSI when going from the proximal colon through the left colon to the rectum, and increased frequencies of MACS in the distal colon and rectum[83]. Our results agree with those previously described by other authors[73].

CONCLUSION

Although early age of onset is a criterion used to identify hereditary CRC, several studies have observed that a significant percentage of cases within this population have MSS tumors. In addition, MACS tumors are present in a substantial proportion. Moreover, when we analyzed the three main molecular pathways and their phenotypic features in early-onset CRC, we observed striking differences between these tumors and late-onset tumors. The theoretical existence of different molecular bases, mainly suggested by the heterogeneous MSS CRC group, has already opened an important new field of research aimed at finding related candidate susceptibility loci. Taken together, these observations support the increasingly clear possibility that early-onset CRC may be a different disease than late-onset CRC, even though they have much in common.

This integrated view of molecular alterations, their associations with disease phenotype and their implications in tumor progression and development will allow a better understanding of the physiopathology of CRC and the identification of new therapeutic targets, and lead to more individualized patient management, in this case, according to the age of onset.

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