Review

Biology and genetics of colorectal cancer

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ABSTRACT

Colorectal cancer is one of the most common malignant tumors. The frequency and potential for prevention put colorectal cancer at the center of attention of oncologists around the world. Malignant transformation is the result of the accumulation of mutations of numerous genes that are critical to regulating cell growth and differentiation, either due to increasing of the rate of mutations or due to the damage of DNA repair mechanisms. In this review, we discuss biology and genetics of colorectal cancer.

KEY WORDS: colorectal neoplasms; cancer genes; genes, tumor suppressing; adenomatous polyposis coli; attenuated familial adenomatous polyposis; colorectal neoplasms, hereditary nonpolyposis

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INTRODUCTION

Colorectal cancer is one of the most common malignant tumors, and in the world there are more than 850000 people annually, and half a million people die of colorectal cancer every year (1). Colorectal cancer incidence begins to rise after 40 years of age, both in men and women. After the age of 50, the frequency begins to increase rapidly. Of all colorectal cancer, 92% are diagnosed in people over the age of 50 and 12.5% of all colorectal cancers are diagnosed in the 8th decade of life (2, 3).

Colorectal cancer is the second most common malignant tumor in men, immediately after lung cancer, with an incidence of 14%. It is also at the second place in women, behind breast cancer, with a frequency of 14%. In 2005, 1610 men and 1217 women were diagnosed with colorectal cancer in Croatia. The incidence rate of newly diagnosed colorectal cancer patients was 75.4 per 100,000 men and 52.9 per 100,000 women. The highest incidence in both sexes is between 80 and 84 years of age (4). In the United States, colorectal cancer continues to be ranked third, both among men and women (2).

Given that the risk of colorectal cancer increases with age, and the population in most highly developed countries shows a tendency of aging, it is clear that the number of people at risk for colorectal cancer today is greater than ever.

Five-year survival of patients with diagnosed colorectal cancer is approximately 60% (5). Understandably, the survival of these patients is significantly improved if malignant disease is diagnosed in an early, localized stage. However, one fifth of patients with colorectal cancer are diagnosed at an advanced stage of illness, when cure is less certain (3).

Most colorectal cancer patients develop metastases over time, most commonly in liver (6, 7). In 30-40% of patients with colorectal carcinoma, metastases are diagnosed only in liver (5-7). Five-year survival of patients with potentially curative liver resection due to colorectal cancer metastases is 25-40% (6), and median survival is, according to various authors, between 24 and 40 months (5). This high incidence of metastasis in the liver resulted

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in changes in treatment to improve the survival rate of patients with colorectal cancer (8), and this is confirmed by recent findings suggesting an increase in survival rates for these patients (9-11).

The frequency and potential for prevention puts colorectal cancer at the center of attention of oncologists around the world. Indeed, digestive cancers are considered to represent 20% of all cancers. Large differences in patient characteristics as well as a wide range of stages at the time of diagnosis and initiation of treatment require a multidisciplinary approach to this malignant disease (5).

BIOLOGY AND GENETICS OF COLORECTAL CANCER

Malignant transformation is the result of the accumulation of mutations of numerous genes that are critical to regulating cell growth and differentiation, resulting either by increasing the rate of mutation or due to damage to DNA repair mechanisms. Carcinoma therefore arises as a result of these changes, enabling advancing malignant cells to grow. According to Knudson's theory, hereditary forms of cancer occur in people with mutations of an allele of recessive tumor genes, after which only one additional somatic mutation can lead to gene inactivation and carcinogenesis. The sporadic forms of cancer need two somatic mutations or the loss of two alleles (12).

In the carcinogenesis process, three categories of genes are involved: oncogenes, tumor suppressor genes and genes that are primarily responsible for the mismatch repair mechanisms, most commonly known as MLH1, MSH2, MSH6 and PMS2. When the protooncogene (a normal human gene associated with growth control of certain tissues) is abnormally activated, it promotes cellular cycle and cell division, facilitating clonal proliferation and such a gene is called an oncogene. Some of the most important mechanisms of oncogenes activation are the translocation of chromosome parts, their amplification or mutation. Oncogenes are dominant because the mutation of only one of alleles is enough to express the effect on the cellular level. Oncogenes, however, are not the only responsible for tumor formation because only 20% of human cancers show oncogene mutations. This is because tumor suppressor genes can stop the cell cycle and malignant transformation even when oncogenes are mutated.

Tumor suppressor genes behave recessively, meaning that the onset of cancer only occurs when loss or mutation occurs with the inactivation of both alleles. If the cells can not repair damaged DNA, the tumor suppressor genes, such as, for example, p53 genes, can block the cell division cycle, stop it at transition from G1 to S phase, thereby providing enough time to repair the damaged gene material, and if the damage is too great, they can trigger programmed cell death - apoptosis. Therefore, this gene is also called the genomic supervisor. In 1991, a tumor suppressor gene was identified on chromosome 5, which is the key to colorectal cancer, and was named APC (adenomatous polyposis coli). It has been found that in colorectal cancer this gene may exhibit the hereditary mutation of one allele (13, 14). Somatic APC gene mutations occur early in the process of the emergence of most neoplastic polyps and cancers (15).

The last group of tumor-related genes is a group of mismatch repair genes (MMRs). These genes encode DNA damage repair processes due to errors in replication or spontaneous loss of base pairs (16). In humans, six genes responsible for this part of DNA repair mechanisms (MMR gene) are described: hMSH2 (chromosome 2p16), hMLH1 (chromosome 3p21), hPMS1 (chromosome 2q31-33), hPMS2 (chromosome 7q11), hMSH6 (chromosome 2p16), and hMSH3 (chromosome 5q11.2-q13.2). In case of inactivation of both copies of these genes, the repair process of damaged DNA is damaged and there are numerous errors in replication of DNA, thereby accelerating the oncogenesis process. The first four mentioned genes are related to the emergence of hereditary nonpolyposis colorectal carcinoma (HNPCC) in 31%, 33%, 2%, and 4% of cases (17, 18).

The genes hMSH2 and hMLH1 are responsible for over 60% of hereditary forms of non-polyposis colorectal cancer which meets the international diagnostic criteria (19). According to some authors (20), described hereditary mutations in one of the four major genes associated with the emergence of HNPCC (MLH1, MSH2, MSH6, And PMS2) can be found in 70-80% of the affected families.

Traditionally, the emergence of cancer is understood as a process that consists of three steps: initiation, promotion and progression. Colorectal cancer is a genetically heterogeneous disease and many changes in the genome are described in the formation of this cancer. It is known that specific environmental factors, primarily nutritional habits, can modify the sequence of occurrences of colorectal cancer (21, 22).

In colorectal cancer patients, the effect of environmental factors is relatively small in

relation to the significance of inherited genetic mutations. Therefore, the risk of colorectal cancer is significantly higher in hereditary forms, for example 100% in polyposis colon syndrome and approximately 85% in hereditary nonpolyposeous colorectal cancer (HNPCC) (23).

So far, numerous studies have been published describing the importance of genetic changes in the etiology of colorectal cancer. Transformation from normal epithelium through adenoma to cancer is associated with the sequence of acquired molecular events. In this course of transformation from normal colon cancer epithelial cells to cancer requires at least 6 to 10 important genetic changes (24).

These changes not only enable uncontrolled cell growth but also provide a basis for increasing the frequency of new mutations. This condition, called gene instability, is crucial for carcinogenesis (25). It accelerates the process of neoplasm formation and increases the probability of creating new mutations. Without achieving genetic instability, the accumulation of new mutations would be too slow, and the onset of cancer probably did not occur during the expected life expectancy of human life (26). In normal cells there are a number of systems for maintaining and preserving genetic integrity. If the genome damage is too large, the protective mechanisms in the cell prevent further dividing and propagation of the damaged DNA and introduce the cell into the programmed death - apoptosis.

Two major categories of genomic instability in colorectal carcinoma have been described. Chromosomal instability is most often present, where DNA damage is caused by structural or numerical chromosome disorders (aneuploidy) (24).

The second basic type of genetic instability is microsatellite instability (MSI), which results in the inability to repair erroneously bound bases resulting from DNA replication (27). Microsatellite are repeating nucleotide sequences that are scattered within the genome and the term microsatellite instability refers to deviations in the number of repeating baseline sequences within a specific genome area in the tumor relative to normal DNA.

Genomic instability indicates a genome condition that favors higher frequency of accumulation of genetic mutations and the consequent emergence of malignant cell transformation. Chromosomal instability is a form of genetic instability in which there are chromosome-level disorders, primarily due to chromosome segregation disorder during cell division, but this form of genomic instability also includes translocation, segmentation duplication and deletion as well as amplification of genes (16). Approximately 70-85% of colorectal cancer is caused by chromosomal instability (28). The earliest observable lesion is a dysplastic aberrant crypt focus (ACF), a microscopic mucosal lesion that precedes the creation of a macroscopic polyp (29). In this sequence of events there are mutations of several genes, such as APC, K-ras, p53 and DCC (28).

Solomon, Voss, and Hall (30) examined the significance of loss of part of chromosome 5 (which was later found to contain APC gene) in colorectal cancer patients. They showed that at least 20% of the cancer showed the loss of one alleles present in normal tissue. Therefore they assumed that the loss of one allele in most cases of colorectal cancer is a key event in progression. They did not record deletions in any other chromosome, suggesting that the loss of part of the chromosome 5 is not a random occurrence. Law and associates (31) described the allelic losses on chromosomes 17 and 18 and showed that these occurrences are more frequent than loss of allele on chromosome 5. Today, it is believed that the mutations responsible for the occurrence of colorectal cancer are affected by these three genes. Locus 5q21 contains the APC gene, which has been changed to about 60% of the colon cancer and 82% of the rectal cancer (27). Other polyps and cancers exhibit microsatellite instability resulting from gene mutations responsible for repairing damage caused by DNA replication.

The inherited mutations of APC genes lead to the emergence of neoplastic polyps in patients with inherited adenomatous polyposis and lead to a high risk of clonal proliferation of epithelial cryptic cells. Today, there is numerous evidence supporting the hypothesis of a multi-step process that can be developed over a decade and which requires at least seven genetic mutations because it is a genetically highly heterogeneous disease (16).

A small proportion of epithelial colorectal cells, that are subject to neoplastic changes, supports the low rate of somatic APC mutations expected in normal epithelial colon cells. Hence, the research of the hereditary colon polyposis syndrome gives strong support to Knudson's "Two Strikes" theory, which was proposed to explain the incidence of both inherited and sporadic variants of tumors (32).

Key changes in chromosomal instability-related carcinoma include a variety of chromosome changes (aneuploidy) and noticeable loss of parts of chromosomes 5q, 18q and 17p, as well as mutations

of K-ras oncogenes. The major genes affected by such losses are APC (on chromosome 5q), DCC, SMAD2 and SMAD4 (on chromosome 18q) and p53 on chromosome 17p. Loss of chromosome parts is associated with instability at the molecular and chromosome levels.

The APC gene ("adenomatous polyposis coli") consists of 15 exons with several functional domains and is therefore highly susceptible to mutations. In humans it is located on the long arm of chromosome 5 (5q21). APC gene is a tumor suppressor gene. It was discovered in 1991 as the gene responsible for the formation of family adenomatous polyposis (FAP). Hereditary mutations of this gene are found in patients with familial adenomatosis polyposis while acquired mutations occur very early in the emergence of sporadic colorectal carcinomas. Inactivation of one allele leads to the formation of microadenoma in the colon, and the inactivation of both alleles results in the formation of macroscopic adenoma (13, 33). APC gene mutations usually result in a shortened protein product. Such a shortened protein product can not be bound to β-catenin, and that complex is responsible for regulating the Wnt signaling pathway in the cell (34). The Wnt signaling pathway is responsible for regulation of proliferation, apoptosis and cell differentiation, such as, for example, in basal cryptal cells in the colon (35). The loss of a functional APC protein can interfere with the normal flow of cell division (36). The normal product of the APC gene binds to kinetohors and this complex is responsible for normal distribution of the gene material during cell division (37). Cells with APC mutations are not able to detect genetic damage and the mitosis continues that can result in further loss of chromosomal material in cells (38).

Studies in patient familiar polyposis coli (FAP), as well as in mice with analog gene mutations, indicate that somatic mutations of APC gene is a key and limiting step in the formation of colorectal cancer (39-41).

K-ras is a protooncogen whose protein product binds to GTP. The mutant gene product of K-ras prevents hydrolysis of active GTP into inactive GDP. Gene K-ras in humans is found on chromosome 12 (12p12). The most common mutations of K-ras genes in colon cancer were found in codons 12, 13 and 61. K-ras gene mutations are found in over 60% of atypical focal points in glandular colonic crypts and in over 35% of atypical adenomas and colorectal carcinomas (42-44).

Gene p53 is located on the chromosome 17 (17p13) and is a tumor-suppressor gene by function. The loss of function of this gene is most commonly attributable to the loss of alleles 17p. The protein product of this gene is an important regulator of expression of other genes that regulate cell division. The function of the protein product of p53 gene is the stimulation of expression of genes that slow down the cell cycle and allow enough time to repair the damaged DNA. In the case of excessive DNA damage, protein product gen 53 induces expression of proapoptotic genes initiating programmed cell death. The amount of p53 gene mutations, whether mutations or loss of heterozygosity, increases with the histological stage of the tumor and thus anomalies are found in 4-26% of adenomas, 50% of adenomas with invasive foci and in 50-75% of colorectal carcinomas (42, 45).

Gene DCC is located on chromosome 18 (18q21) and the allele loss at this site is found in 60% of colorectal carcinomas (46). Gene DCC encodes a 170-190 kDa protein, which participates in cell adhesion and serves as a transmembrane receptor, which in the absence of its ligand (netrin-1) induces apoptosis (47).

Close the DCC gene on the same chromosome are the genes SMAD2 and SMAD4 involved in the TGF-ß signaling process, and are important in regulating cell growth and apoptosis (45, 48). In the normal mucosa, DCC gene is active, while in cancer it is significantly reduced or even absent (49). It is considered that the loss of function of this gene causes the transition to invasive cancer. Therefore DCC is today among the most important molecular prognostic markers of colorectal cancer (50).

Disorder of genes responsible for the repair of damages caused by replication of the DNA is the second form of genomic instability (16, 20). First, there is a disorder in damaged DNA repair processes, resulting in a genetic instability manifested by a high rate of subtle mutations throughout the genome. Damaged genomic repair mechanisms allow damages of tumor suppressor genes or occurrence of chromosomal translocation. Furthermore, increased gene inactivation due to present mutations may contribute to an increased rate of chromosomal aberrations in cells with damaged DNA repair mechanisms. Also, mutations can affect critical genes that allow the growth of the transformed cells. Finally, there is evidence that impaired protection against endogenous and exogenous DNA damage and consequent mutation can lead to instability of genomes in colon cancer cells (20).

The characteristics of microsatellite instability are damage to the DNA replication error repair

mechanism, which can be detected at the molecular level by tracking changes in recurring DNA sequences that can occur throughout the genome, called DNA microsatellite. Replication instability of microsatellite is a fundamental feature of cancer with expressed microsatellite instability. This instability, which is the dominant marker of HNPCC, exists in approximately 15-25% of sporadic colorectal carcinomas.

According to international criteria, a high degree of microsatellite instability (MSI-H) is defined as instability in two or more of five sites or at 30-40% of all examined microsatellite sites, while lower expression instability is defined as low (MSI-L) (20).

Colorectal carcinomas with high-grade microsatellite instability (MSI-H) comprise a tumor group dominantly occupying the proximal colon (from cecum to lienal flexure), containing a diploid amount of DNA, a high degree of differentiation and is associated with a female gender and has a better survival. These characteristics distinguish them from other cancers, namely low-level microsatellite instability (MSI-L) and microsatellite stable tumors (MSS). Most of the cancers with high levels of microsatellite instability are caused by the inactivation of the MLH1 gene. Although the incidence of low-level microsatellite instability (MSI-L) carcinomas is similar to that of high-level microsatellite instability carcinomas (MSI-H), immunohistological assays and gene mutation analyzes in the low-level microsatellite instability carcinoma group, discovered no MLH1, MSH2, MSH6 or MSH3 gene involvement. Therefore, on the basis of clinical and histological features alone, it is not possible to distinguish low-grade microsatellite instability (MSI-L) carcinomas from microsatellite stable carcinomas (MSS) (20).

CLINICAL IMPORTANCE OF GENETIC MUTATIONS

Knowing the genetic basis of colorectal cancer has important clinical implications. Before basic genetic disorders in colorectal cancer were discovered, it was known that proximal colon cancers (from cecum to lienal flexure) have predominantly normal cytogenetic structure, diploid DNA content, slower growth, lower metastasis frequency and better prognosis than distal carcinomas, i.e. those distal from the lienal flexure (20). Furthermore, the incidence of extracolonic carcinomas is higher in patients with proximal colorectal carcinomas and in first line relatives of patients with proximal colon cancer. Most of the distal colon and rectum cancer arises on the basis of a chromosomal instability with a marked loss of heterozygosity of tumor suppressor genes, while proximal colon cancers are predominantly a consequence of the damage of genes responsible for the repair of damaged DNA.

FAMILIAL ADENOMATOUS POLYPOSIS (FAP)

Familial Adenomatous Polyposis (FAP) is a hereditary disease that is transmitted by autosomal dominance and is characterized by the development of several hundred or even thousands of adenomatous polyps in the entire colon. Clinical diagnosis is based on histological confirmation of at least 100 adenomas. However, since more and more people are subjected to colorectal cancer screening, and more frequently genetic testing is carried out (although not often enough), the criteria of the number of polyps becomes relative. However, in the absence of a family history of hereditary adenomatous polyposis of the colon, the rule of existence of at least 100 polyps represents the most common basis of diagnosis (51).

An important feature of this syndrome is the fact that at least one of these polyps progresses into invasive adenocarcinoma if no preventative proctocolectomy is performed. The disease has a high penetration, with probability of 50% in affected families. Approximately 20% of patients with hereditary adenomatous polyposis do not have family history and therefore the disease may be attributed to spontaneous gene mutations (52).

Attenuated Familial Adenomatous Polyposis (AFAP) is a form of FAP syndrome that has only recently been recognized and described (53, 54). The largest number of patients with this form of hereditary polyposis has up to 450 adenomas that are primarily located in the right colon, proximal of the lienal flexure, and which are most commonly flat. These polyps are most commonly diagnosed in the middle of the fifth decade of life, and cancers are found usually during the sixth decade. Thus, the diagnosis of polyps and carcinomas in syndrome of attenuated hereditary polyposis is set about 10-15 years later than in the FAP syndrome. Obviously, due to the absence of recognition of this syndrome by patients and doctors, a relatively small number of patients are subjected to voluntary monitoring, which leads to subsequent diagnosis (55).

There is a correlation between the APC gene mutation site and the clinical manifestation of the disease. The APC gene consists of 15 exons. The exact location of the hereditary mutation is associated

with the specific expression of the disease. To date, 34 mutations that lead to AFAP syndrome have been described and all of them are located either before codon 436 or after codon 1596 of the APC gene. In contrast, mutations that cause the classic form of FAP syndrome are located in the central region of the APC gene and the mutations between codons 1250 and 1464 cause the particularly severe form of polyposis (51).

SYNDROME OF HEREDITARY NONPOLYPOID COLORECTAL CANCER (HNPCC)

Despite its name, polyps are a feature of HNPCC syndrome. Approximately 8-17% of the first relatives of patients with HNPCC syndrome have polyps on colonoscopic screening (56). In their work, DeFrancisco and Grady (57) described the genes responsible for HNPCC syndrome: MLH1, MSH2, MSH6, MLH3, PMS1, PMS2, TGFBR2, and EXO1.

A relatively large number of patients with mutations of these genes develop colorectal cancer within 3 years of the colonoscopy without a tumor, indicating that the sequence of malignant adenoma disease to cancer in these patients is accelerated and can be less than 3 years. HNPCC-related carcinomas are inherited dominantly with penetration of 70-80% (58) to almost 100% (59).

REFERRENCES

1. Ries LAG, Eisner MP, Kosary LC. SEER Cancer Statistics Review, 1973-1997. Bethesda, MD: National Cancer Institute; 2000.
2. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007;57(1):43-66.
3. American Cancer Society. Cancer facts and figures 2006. Atlanta, Georgia:2006.
4. Hrvatski zavod za javno zdravstvo. Incidencija raka u Hrvatskoj. Bilten br 30. Zagreb:2005.
5. Benson AB, 3rd. Epidemiology, disease progression, and economic burden of colorectal cancer. J Manag Care Pharm. 2007;13(6 Suppl C):S5-18.
6. Doko M, Zovak M, Ledinsky M, Mijic A, Peric M, Kopljar M, Culinovic R, Rode B, Doko B. Safety of simultaneous resections of colorectal cancer and liver metastases. Coll Antropol. 2000;24(2):381-390.
7. Kopljar M, Brkljacic B, Doko M, Horzic M. Nature of Doppler perfusion index changes in patients with colorectal cancer liver metastases. J Ultrasound Med. 2004;23(10):1295-1300.
8. Penna C, Nordlinger B. Colorectal metastasis (liver and lung). Surg Clin North Am. 2002;82(5):1075-1090, x-xi.
9. Fernandez FG, Drebin JA, Linehan DC, Dehdashti F, Siegel BA, Strasberg SM. Five-year survival after resection of hepatic metastases from colorectal cancer in patients screened by positron emission tomography with F-18 fluorodeoxyglucose (FDG-PET). Ann Surg. 2004;240(3):438-447; discussion 447-450.
10. Pawlik TM, Scoggins CR, Zorzi D, Abdalla EK, Andres A, Eng C, Curley SA, Loyer EM, Muratore A, Mentha G, Capussotti L, Vauthey JN. Effect of surgical margin status on survival and site of recurrence after hepatic resection for colorectal metastases. Ann Surg. 2005;241(5):715-722, discussion 722-714.
11. Adam R, Delvart V, Pascal G, Valeanu A, Castaing D, Azoulay D, Giacchetti S, Paule B, Kunstlinger F, Ghemard O, Levi F, Bismuth H. Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg. 2004;240(4):644-657; discussion 657-648.
12. Knudson AG, Jr. Hereditary cancer, oncogenes, and antioncogenes. Cancer Res. 1985;45(4):1437-1443.
13. Fearnhead NS, Britton MP, Bodmer WF. The ABC of APC. Hum Mol Genet. 2001;10(7):721-733.
14. Uhrhammer N, Bignon YJ. Report of a family segregating mutations in both the APC and MSH2 genes: juvenile onset of colorectal cancer in a double heterozygote. Int J Colorectal Dis. 2008;23(11):1131-1135. Epub 2008 Jul 1116.
15. Alrawi SJ, Schiff M, Carroll RE, Dayton M, Gibbs JF, Kulavlat M, Tan D, Berman K, Stoler DL, Anderson GR. Aberrant crypt foci. Anticancer Res. 2006;26(1A):107-119.
16. Pećina-Šlaus N, Beroš V, Nikuševa Martić T, Bulić-Jakuš F. Genomic instability of the APC gene found in glioblastoma. In: Glascow EJ, editor. New research in genomic instability: Nova Science Publishers; 2007. p. 121-137.
17. Lynch BM, Baade P, Fritschi L, Leggett B, Owen N, Pakenham K, Newman B, Aitken JF. Modes of presentation and pathways to diagnosis of colorectal cancer in Queensland. Med J Aust. 2007;186(6):288-291.
18. Foulkes WD, Thiffault I, Gruber SB, Horwitz M, Hamel N, Lee C, Shia J, Markowitz A, Figer A, Friedman E, Farber D, Greenwood CM, Bonner JD, Nafa K, Walsh T, Marcus V, Tomsho L, Gebert J, Macrae FA, Gaff CL, Paillerets BB, Gregersen PK, Weitzel JN, Gordon PH, MacNamara E, King MC, Hampel H, De La Chapelle A, Boyd J, Offit K, Rennert G, Chong G, Ellis NA. The founder mutation MSH2*1906G->C is an important cause of hereditary. Am J Hum Genet. 2002;71(6):1395-1412. Epub 2002 Nov 1326.
19. Nystrom-Lahti M, Kristo P, Nicolaides NC, Chang SY, Aaltonen LA, Moisio AL, Jarvinen HJ, Mecklin JP, Kinzler KW, Vogelstein B, et al. Founding mutations and Alu-mediated recombination in hereditary colon cancer. Nat Med. 1995;1(11):1203-1206.
20. Peltomaki P. Role of DNA mismatch repair defects in the pathogenesis of human cancer. J Clin Oncol. 2003;21(6):1174-1179.
21. Willett WC, Stampfer MJ, Colditz GA, Rosner BA, Speizer FE. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med. 1990;323(24):1664-1672.
22. Luchtenborg M, Weijenberg MP, de Goeij AF, Wark PA, Brink M, Roemen GM, Lentjes MH, de Bruine AP, Goldbohm RA, van 't Veer P, van den Brandt PA. Meat and fish consumption, APC gene mutations and hMLH1 expression in colon and rectal cancer: a prospective cohort study (The Netherlands). Cancer Causes Control. 2005;16(9):1041-1054.
23. Kadiian K, Stoinov S, Penchev P, Mikhova A, Damianov D, Aleksandrova A, Nedin D, Vladimirov B, Draganov V, Tankova L, Gerova V, Tsolova N, Churchev I, Nakov N, Tsancheva M. [Polyposis of the colon and cancer]. Khirurgiia (Sofiia). 2004;60(1):42-44.
24. Rajagopalan H, Lengauer C. Aneuploidy and cancer. Nature. 2004;432(7015):338-341.

25. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature. 2001;411(6835):366-374.
26. Loeb LA. Mutator phenotype may be required for multistage carcinogenesis. Cancer Res. 1991;51(12):3075-3079.
27. Jass JR, Whitehall VL, Young J, Leggett BA. Emerging concepts in colorectal neoplasia. Gastroenterology. 2002;123(3): 862-876.
28. Grady WM. Genomic instability and colon cancer. Cancer Metastasis Rev. 2004;23(1-2):11-27.
29. Takayama T, Ohi M, Hayashi T, Miyanishi K, Nobuoka A, Nakajima T, Satoh T, Takimoto R, Kato J, Sakamaki S, Niitsu Y. Analysis of K-ras, APC, and beta-catenin in aberrant crypt foci in sporadic. Gastroenterology. 2001;121(3):599-611.
30. Solomon E, Voss R, Hall V, Bodmer WF, Jass JR, Jeffreys AJ, Lucibello FC, Patel I, Rider SH. Chromosome 5 allele loss in human colorectal carcinomas. Nature. 1987;328(6131):616-619.
31. Law DJ, Olschwang S, Monpezat JP, Lefrancois D, Jagelman D, Petrelli NJ, Thomas G, Feinberg AP. Concerted nonsyntenic allelic loss in human colorectal carcinoma. Science. 1988;241(4868):961-965.
32. Knudson AG. Antioncogenes and human cancer. Proc Natl Acad Sci U S A. 1993;90(23):10914-10921.
33. Pecina-Slaus N. [Tumor suppressor genes with special emphasis on the APC tumor suppressor gene]. Lijec Vjesn. 1998;120(7-8):219-227.
34. Cadigan KM, Liu YI. Wnt signaling: complexity at the surface. J Cell Sci. 2006;119(Pt 3):395-402.
35. Kuhnert F, Davis CR, Wang HT, Chu P, Lee M, Yuan J, Nusse R, Kuo CJ. Essential requirement for Wnt signaling in proliferation of adult small intestine. Proc Natl Acad Sci U S A. 2004;101(1):266-271. Epub 2003 Dec 2026.
36. Fodde R, Kuipers J, Rosenberg C, Smits R, Kielman M, Gaspar C, van Es JH, Breukel C, Wiegant J, Giles RH, Clevers H. Mutations in the APC tumour suppressor gene cause chromosomal instability. Nat Cell Biol. 2001;3(4):433-438.
37. Green RA, Wollman R, Kaplan KB. APC and EB1 function together in mitosis to regulate spindle dynamics and. Mol Biol Cell. 2005;16(10):4609-4622. Epub 2005 Jul 4619.
38. Draviam VM, Shapiro I, Aldridge B, Sorger PK. Misorientation and reduced stretching of aligned sister kinetochores promote. Embo J. 2006;25(12):2814-2827. Epub 2006 Jun 2818.
39. Ichii S, Horii A, Nakatsuru S, Furuyama J, Utsunomiya J, Nakamura Y. Inactivation of both APC alleles in an early stage of colon adenomas in a patient. Hum Mol Genet. 1992;1(6):387-390.
40. Levy DB, Smith KJ, Beazer-Barclay Y, Hamilton SR, Vogelstein B, Kinzler KW. Inactivation of both APC alleles in human and mouse tumors. Cancer Res. 1994;54(22): 5953-5958.
41. Luongo C, Moser AR, Gledhill S, Dove WF. Loss of Apc+ in intestinal adenomas from Min mice. Cancer Res. 1994;54(22):5947-5952.
42. Leslie A, Carey FA, Pratt NR, Steele RJ. The colorectal adenoma-carcinoma sequence. Br J Surg. 2002;89(7):845-860.
43. Jen J, Powell SM, Papadopoulos N, Smith KJ, Hamilton SR, Vogelstein B, Kinzler KW. Molecular determinants of dysplasia in colorectal lesions. Cancer Res. 1994;54(21):5523-5526.
44. Cheng L, Lai MD. Aberrant crypt foci as microscopic precursors of colorectal cancer. World J Gastroenterol. 2003;9(12):2642-2649.
45. Fearon ER, Vogelstein B. A genetic model for colorectal tumorigenesis. Cell. 1990;61(5):759-767.
46. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, Nakamura Y, White R, Smits AM, Bos JL. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988;319(9):525-532.
47. Martin M, Simon-Assmann P, Kedinger M, Mangeat P, Real FX, Fabre M. DCC regulates cell adhesion in human colon cancer derived HT-29 cells and associates with ezrin. Eur J Cell Biol. 2006;85(8):769-783. Epub 2006 Jun 2008.
48. Fearon ER, Cho KR, Nigro JM, Kern SE, Simons JW, Ruppert JM, Hamilton SR, Preisinger AC, Thomas G, Kinzler KW, et al. Identification of a chromosome 18q gene that is altered in colorectal cancers. Science. 1990;247(4938):49-56.
49. Calvert PM, Frucht H. The genetics of colorectal cancer. Ann Intern Med. 2002;137(7):603-612.
50. Fodde R, Smits R, Clevers H. APC, signal transduction and genetic instability in colorectal cancer. Nat Rev Cancer. 2001;1(1):55-67.
51. Nivatvongs S. Benign neoplasms of the colon and rectum. In: Gordon PH, Nivatvongs S, editors. Neoplasms of the colon, rectum and anus. New York, London: Informa Healthcare; 2007.
52. Rustin RB, Jagelman DG, McGannon E, Fazio VW, Lavery IC, Weakley FL. Spontaneous mutation in familial adenomatous polyposis. Dis Colon Rectum. 1990;33(1):52-55.
53. Spirio L, Olschwang S, Groden J, Robertson M, Samowitz W, Joslyn G, Gelbert L, Thliveris A, Carlson M, Otterud B, et al. Alleles of the APC gene: an attenuated form of familial polyposis. Cell. 1993;75(5):951-957.
54. Lynch HT, Smyrk T, McGinn T, Lanspa S, Cavalieri J, Lynch J, Slominski-Castor S, Cayouette MC, Priluck I, Luce MC. Attenuated familial adenomatous polyposis (AFAP). A phenotypically and genotypically distinctive variant of FAP. Cancer. 1995;76(12):2427-2433.
55. Hernegger GS, Moore HG, Guillem JG. Attenuated familial adenomatous polyposis: an evolving and poorly understood entity. Dis Colon Rectum. 2002;45(1):127-134; discussion 134-126.
56. Lynch HT, Smyrk T. Hereditary nonpolyposis colorectal cancer (Lynch syndrome). An updated review. Cancer. 1996;78(6):1149-1167.
57. DeFrancisco J, Grady WM. Diagnosis and management of hereditary non-polyposis colon cancer. Gastrointest Endosc. 2003;58(3):390-408.
58. Cunningham C, Dunlop MG. Molecular genetic basis of colorectal cancer susceptibility. Br J Surg. 1996;83(3):321-329.
59. Piepoli A, Santoro R, Cristofaro G, Traversa GP, Gennarelli M, Accadia L, Siena D, Bisceglia M, Lynch HT, Peltomaki P, Andriulli A. Linkage analysis identifies gene carriers among members of families with. Gastroenterology. 1996;110(5): 1404-1409.