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Chapter

A Genetic Perspective on Colorectal Cancer Progression

Lenuce Ribeiro Aziz Ydy, Willian Ricardo Camarço-Silva and Wilson Vilela Medeiros-Filho

Abstract

The colorectal cancer is one of most frequent neoplasia in adult population. Since was described the adenoma-carcinoma sequence for the first time in 1978, the elucidation of the molecular mechanisms involved in the pathogenesis of colorectal cancer became studied. The study of colorectal cancer has been one of the most important elements for understanding the mechanisms involved in the genesis of malignant neoplasms. Several genes, like DCC, APC, p53 were identified as participants of the adenoma-carcinoma. The annexin A1 protein (ANXA1) is related with some types of tumor and its study in colorectal cancer in scientific literature is been done, but discreetly yet. The increasing advancement in molecular biology research have contributes for understanding the carcinogenesis, with the possibility of detecting earlier pre-malignant lesions and a proper diagnosis, more over it allow the development an efficient therapy.

Keywords: colorectal cancer, molecular biology, carcinogenesis

1. Introduction

Colorectal cancer (CCR) is the third most common cancer in men, the second in women and the third most prevalent cause of mortality in the world. It was estimated more than 1.8 million new cases in 2018 according to American Institute for Cancer Research and Continuous Update project panel. It is linked to the transition nutrition to the western lifestyle, consuming processed meat, red meat and alcoholic drinks, greater body fatness and adult height increase the risk of the disease. The incidence of the disease continues to rise especially in low and middle income countries and it is considered one of the clearest markers for rapid societal and economic changes that are associated with cancer development [1].

Genetic knowledge is essential for understanding of carcinogenic colorectal cancer, and can develop strategies for prevention, diagnosis and treatment. A list of genes in which mutations are capable of interfering with both cancer creation and treatment, has grown a lot in recent years, helping to understand risks for cancer formation and identifying several promising therapeutic targets. Today focused on a best treatment, but research on colorectal cancer genetics began with a focus on diagnosis, much of our understanding of pathogenesis came from study of hereditary syndromes of colorectal diseases that advanced into cancer, showing a huge diversity in types of colorectal cancer and genetic involvement.

In 1882 W. Harrison Cripps associated in his work that multiple intestinal polyposis had hereditary nature and also potentially malignant nature. Subsequently in 1913 Aldred S. Warthin reported on 1600 cases of carcinoma treated at University of Michigan for 19 years, collecting detailed family histories of approximately 500 patients and mapping a predisposition to gastrointestinal and endometrial carcinogenesis of three generations. In 1950, Eldon J. Gardner at University of Utah conducted a long genetic study in patient families with multiple polyps and established a link between this event and a predisposition to carcinomatosis only in 1986 Herrera et al. described a case of a patient with polyposis and multiple carcinomatosis, with an amputation in a long arm of chromosome 5, suggesting a location of tumor suppressor gene. Subsequent studies in families with polyps have identified the 5q21 region as adenomatous polyposis coli or APC gene. Since then, we have identified numerous genetic defects and genetic expressions showing a diversity of mutations with distinct pathways of progression [2].

There have been significant advances in the last years and more than understanding the risk factors for CCR, recent progress in the field of molecular biology, has allowed us to identify the oncogenesis basis to the development of the disease. Then apply these knowledge in the research of new drugs that lead to better outcomes even in the advanced disease.

2. Molecular basis of carcinogenesis in colorectal cancer

In medical practice, patients with cancer present with great frequency, clinical evolution in a differentiated way in response to the treatment performed. As a result, there is a high margin of uncertainty as to the effectuation of the treatment performed, not infrequently counting initially favorable prognostic evaluations [3].

Cancer results from a long process of at least three phases: initiation, promotion and progression, which reflect accumulated genetic alterations, responsible for the transformation of normal cells into neoplastic cells. The mechanisms of transformation of a normal cell into neoplastic involve a number of genetic and molecular events that affect proliferation and differentiation. In the pathogenesis of neoplastic processes, two groups of genes are involved: proto-oncogenes, which stimulate cell growth and impede differentiation, and tumor suppressor genes, which promote differentiation and limit cell proliferation. The imbalance in the regulation of this system, through the activation of proto-oncogenes or loss of the function of tumor suppressor genes, can lead to the uncontrolled proliferation of cells and to the accumulation of successive genetic abnormalities characteristic of neoplastic cells [4–7].

The development of cancer (oncogenesis) results from mutations in one or more genes, responsible for the regulation of cell growth and programmed cell death called apoptosis (**Figure 1**) [8]. When cancer occurs as part of a hereditary cancer syndrome, the initial mutation causing the cancer is inherited through germ lineage. However, most cancers are sporadic because mutations occur in a single somatic cell, which then divides and proceeds to develop cancer [9].

Considering a frequency of 10-10 replication errors per DNA basis, cell division, and about 1015 cell divisions over the life span of an adult, only replication errors would result in thousands of mutations in the DNA of the genome [8].

Once initiated, a cancer progresses through additional accumulation of genetic damage through mutations in maintenance genes, which encode the DNA repairing cellular machinery. Changes in these genes produce mutations in increasing numbers, leading to failures in controlling cell proliferation and repairing DNA damage. In this way, the original clone of neoplastic cells functions as a reservoir of genetically unstable cells, known as cancer stem cells. These give rise to multiple

underlining of varying degrees of malignancy, each carrying a set of mutations. In this context, cancer is a multifactorial disease with an important genetic component, and mutations are central to its etiology and progression [8] (**Figure 2**).

The classical CCR carcinogenesis model is based on the adenoma-carcinoma sequence in which tumor onset occurs from a sequential and progressive process. This involves the activation of oncogenesis (K-ras) and the inactivation of tumor suppressor genes (APC, DCC, p53) [10, 11]. This model of carcinogenesis, where there is chromosomal instability, is usually found in the distal segments of the colon and rectum [11]. The adenoma-carcinoma sequence was described for the first time by Hill et al. (**Figure 3**) [12].

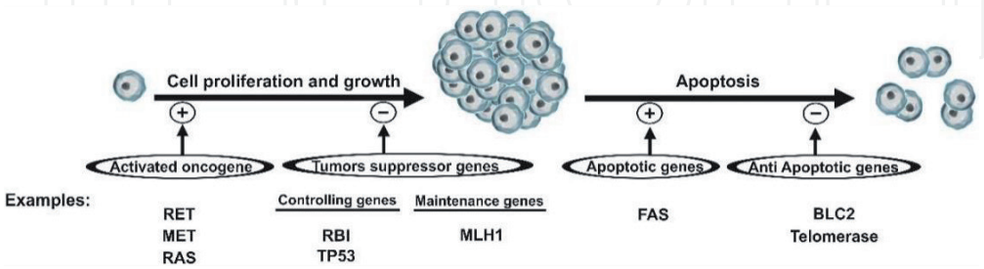


Figure 1.
Mechanism of oncogenesis. General scheme for mechanism of oncogenesis by proto-oncogene activation, loss of tumor suppressor gene expression, activation of anti-apoptotic genes or loss of pro-apoptotic gene expression. The effect of the genes that induce a process is shown as +, while the effect of the genes that suppress a process is shown as −. Modified from Thompson and Thompson [8].

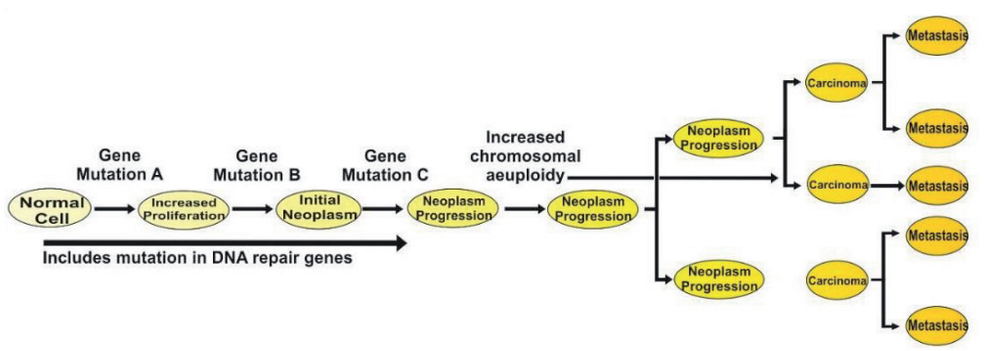


Figure 2.
Stages in the evolution of cancer. Increasing degrees of abnormalities are associated with sequential loss of tumor suppressor genes from various chromosomes and activation of proto-oncogenes, with or without a defect, concomitant in DNA repair. Modified from Thompson and Thompson [8].

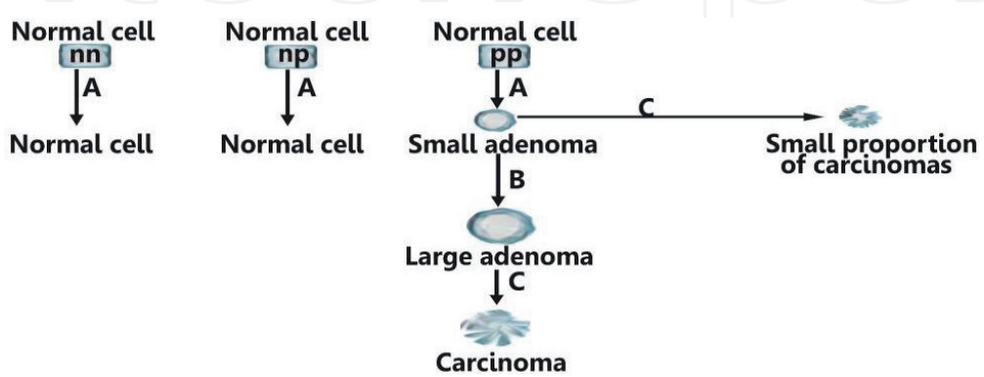


Figure 3.
The adenoma-carcinoma sequence. Postulated mechanism for progression from normal tissue to adenoma to carcinoma. n: normal gene; p: adenoma gene (recessive), so that cell pp: is adenoma-prone. A: environmental agent causing adenomas only in adenoma-prone cell. B: environmental agent causing adenomas to grow. C: agent causing adenomas to develop into carcinomas. Modified from Hill et al. [12].

In the colorectal carcinogenesis, there are a complex interaction between environmental and lifestyle factors and multiple molecular pathways contributes to its occurrence. Three different molecular mechanisms are implicated in colorectal carcinogenesis: chromosomal instability (CIN), genetic instability (GIN) and the serrated pathway. However, although they differ at the beginning of the chain of events, their signaling pathway, implicated in the transformation of the normal epithelial colorectal cell to the neoplastic one, appear to be similar and converge to the clinical and pathological manifestation of the disease. These genetic mechanisms can be acquired after birth and the occurrence of cancer is called sporadic or they can be inherited from the genitors and in this case is called hereditary. In the recent past, only clinical and pathological manifestations were considered when proposing the optimal treatment. However, after the understanding of the patterns implicated in the carcinogenesis, the tumors could be classificated according to molecular standards and individual treatment schemes were developed [13].

2.1 Chromosomal instability

The most frequent model of phenotype group in colorectal cancer are allelic losses in the short arm of chromosome 17 and 8 and in the long arm of chromosomes 5, 18 and 22, being approximately 80% of the sporadic form and are related to mutations in tumor suppressor genes of TP53 genes, APC, SMAD2, and SMAD4.

The first major accepted model for cancer development in colon was described by Fearon and Vogelstein in 1990. The majority of the sporadic CCR tumors originates from premalignant precursor lesions known as polyps, which over time progress to clinically relevant tumors. In this model, the sequence of events leading from the adenoma (polyps) to carcinoma was based on mutation on APC and TP53 genes [13, 14].

The proto-oncogene K-ras (Kirsten-ras) tumor suppressor genes, APC protein (adenomatous polyposis coli), DCC protein (deleted in colorectal cancer) and TP53; and DNA repair or mismatch repair genes (MSH2, MLH1, PMS1, PMS2 and MSH6) are fundamental in development of CCR. Repetitive nucleotide sequences form approximately 25–40% of the DNA molecule being observed several times across the genome as dispersed replicates and tandem or satellite replicates [15]. These replicates can be classified according to the extension of the repetitive sequence in: satellite, minisatellite and microsatellite, depending on the number of nucleotides [16].

Most of the cases of CCR originate from polyps, but it was evidenced that about 45% of the tumors located in the proximal colon originated from epithelium without preexisting polyps, being considered new cancer [17]. In this model of carcinogenesis, which affects 10–15% of cases of sporadic CCR, instead of chromosomal instability there would be genomic instability due to mutations of DNA repair proteins, a phenomenon known as microsatellite instability (IMS) [18]. This pathway of colorectal carcinogenesis due to chromosomal instability is more frequently observed in tumors in the proximal colon, presenting characteristic histological features, being diploid, exophytic growth, worse histological grade, greater tendency to mucus production and lower mutation index in the TP53 gene, and paradoxically, they are associated with a better prognosis [18, 19].

2.2 Microsatellite instability

DNA is a molecule that often undergoes changes through loss of segments, mutations that occur during the process of cell division. To correct these changes, it has proteins with the function of performing the repairs necessary to maintain its integrity. These proteins are produced from some genes known as repair (mismatch

repair genes—MMR) and this function is carried out continuously, preserving the cellular tissues [20–22]. The hMLH1 gene is located on chromosome 3p21-23 [23, 24], hMSH2 on chromosome 2p21 [25–27] and hMSH6 is on 2p16 [28].

In hereditary CCR there are two genetic pathways of carcinogenesis: a chromosomal instability pathway, which occurs in PAF (familial adenomatous polyposis), where the patient inherits a mutation of the APC (adenomatous colonic polyposis) tumor suppressor gene, and DNA hypermutability pathway, which occurs in HNPCC (inherited non-polyposis colorectal cancer) in which the inherited genetic change is the inactivation of one of the alleles of genes involved in DNA repair (hMSH2 and hMLH1 genes). However, other genes are involved in colorectal carcinogenesis, such as K-ras gene, DCC gene, Tp53 gene, etc. [29].

DNA is a molecule that often undergoes changes through loss of segments, mutations that occur during the process of cell division. To correct these changes, it has proteins with the function of performing the repairs necessary to maintain its integrity. These proteins are produced from some genes known as repair (mismatch repair genes—MMR) and this function is carried out continuously, preserving the cellular tissues [20–22]. The hMLH1 gene is located on chromosome 3p21-23 [23, 24], hMSH2 on chromosome 2p21 [25–27] and hMSH6 is on 2p16 [28].

MMRs have the function of recognizing the occurrence of the mutation and blocking cell division in order to prevent the emergence of a defective cell line, which is done by inducing cell death (apoptosis) or performing DNA repair. For the latter, these proteins remove a segment of DNA containing the change and insert a new segment containing the right sequence, based on the "template" of the complementary DNA [30].

The failure of these proteins to function will cause a great instability in the genome, that is, defects in the sequence of base pairs occurring at random in DNA replication cannot be adequately repaired, generating an accumulation of genetic abnormalities that favor the emergence of cancer [30].

A genetic instability that appears in 12–15% of CCR cases, named MSI (microsatellite instability) as a result of a mismatch repair (MMR), what leading to the accumulation of mutations in genes controlling cell cycle and apoptosis (TGFBRII, BAX or CASPASE5) [31].

Cells with changes in MMRs are not able to correctly repair errors during DNA replication. Because of their repetitive structure, microsatellite regions in DNA are particularly prone to these repair errors [32, 33]. The DNA of cells of certain tumors presents differences in the number of repetitive units in one or more microsatellites, when compared to the same microsatellites in the DNA of normal cells, a fact called microsatellite instability (MSI). as positive for replication errors, that is, RER (+) [34].

More than 90% of HNPCC patients present RER (+), while about 15% of sporadic CCRs present this genetic trait [30].

Repair proteins in their normal state form heterodimers [35–38]. MSH2 dimerizes with MSH6 forming the MutSα [38] functional complex, and MLH1 dimerizes with PMS2 to form MutLα [37, 39]. It has been shown that MSH2 and MLH1 proteins are obligatory parts of their respective heterodimers [40–42]. Their abnormalities may result in a proteolytic degradation of their dimers and consequently loss of both mandatory and secondarily associated proteins, the exception includes only MLH1 mutations, when the mutations result in the antigenically activation of the mutated MLH1 protein, which may be the loss of PMS2 only. The reverse, however, is not true, when mutation occurs in the genes of secondary proteins, for example, in MSH6 and PMS2, loss of MSH2 and MLH1 proteins that may not occur, inasmuch as other proteins compensate the function of the secondary proteins, such as MSH3, MLH3 and PMS1. In effect, mutations of MLH1 or MSH2 routinely cause loss of MLH1/PMS2 or MSH2/MHS6, respectively, while mutations of PMS2 or MSH6 cause isolated loss of PMS2 or MSH2 only [43].

Figure 4 shows the model of DNA repair proteins in patients with colorectal cancer [44].

Studies performed in CCR demonstrated a positivity index for greater microsatellite instability in young patients or located in proximal segments of the colon. A study restricted to rectum tumors, the incidence of repair errors was only in 2% of cases, confirming the relationship between microsatellite instability and tumors located in the right or transverse colon [45]. The CCR associated with repair errors tend to present the same location and biological behavior independent of their sporadic or hereditary nature (HNPCC) [45].

2.3 Serrated pathway

The serrated pathway was first described by Longacre and Fenoglio-Preiser in 1990 and differs from the classical adenoma-carcinoma sequence one because in this way there is the participation of other genetic alterations other than chromosomal instability and KRAS mutations like BRAF mutations and gene promoter hypermethylation. But in the serrated pathway, microsatellite instability can also be detected.

The serrated polyps are characterized by glandular serration in which the colonic epithelial crypts show luminal "saw-toothed" pattern. The nomenclature is not well established but the World Health Organization in 2010 classified them into three main groups: hyperplastic polyps, sessile serrated adenomas/polyps and traditional serrated adenomas [46].

Genetically, carcinoma arising from serrated polyps are MSI-H and shows epithelial serrations, clear, eosinophilic and abundant cytoplasm, vesicular nuclei, absence of necrosis, mucin production and presence of cell balls and rods. The finding of serrated lesion in the peripheral of an invasive carcinoma also leads to the diagnostic of this pathway.

Serrated adenocarcinoma is found in about 10% of sporadic colorectal cancers and is originated in the serrated polyp-carcinoma pathway. In this way, hyperplastic polyps now are recognized as neoplastic lesions because they may predispose

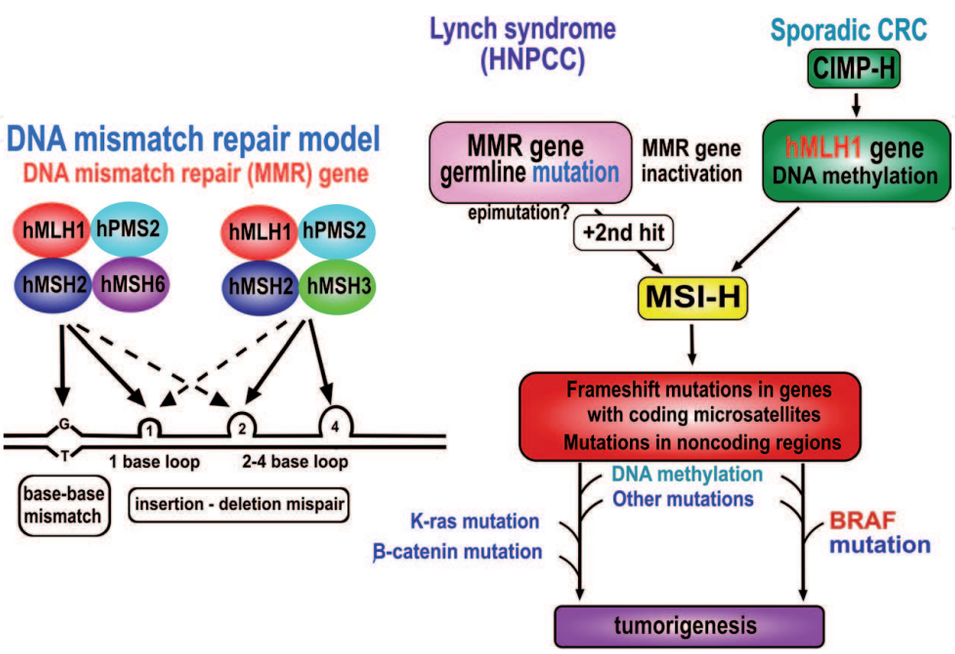


Figure 4.
Model of DNA repair proteins and molecular pathways for CCR with microsatellite instability. Modified from Kohzoh and Yamamoto [44].

to cancer in a sequence in which they progress to serrated adenomas and then to colorectal cancer in at about 7 years. It is not clear why only a few groups of hyperplastic polyps, mainly the ones located in the right colon, will progress to carcinoma and the answer is probably dependent on the genetic findings not elucidated until now. A great number of studies have shown that the right colon is not the same organ as the left colon and the right-sided cancer tends to be more aggressive and this difference is caused by the difference of genetic standard between the sides.

The clinical management of hyperplastic polyps and serrated polyps is essential for avoiding the carcinoma transformation. The most important procedure for prophylaxis is the complete removal of these polyps in colonoscopy and the subsequent surveillance but it is not well established how to follow up. Just for comparison, in the classical adenomatous polyps, the size, number and histological variants (if tubular, villous or tubulovillous) are taken in account to determine the interval of surveillance and this knowledge is more than a decade old. For serrated polyps, as the understanding of this pattern of via is recent, the follow up is not clear hence studies have not shown yet which features are important to determine the risk of progression of these lesions. Moreover, the majority of serrated polyps will not progress to carcinoma and studies answering why are not yet available. A few studies have demonstrated that sessile serrated lesions larger than 10 mm are at high risk for carcinoma progress. But despite the lack of information and in order to prevent cancer arising via serrated pathway, the complete removal of serrated polyps is the goal in these cases.

If there are significant differences regarding the genetic markers and pathological findings in serrated pathway, it is expected to have differences in the presentation of the disease and response to therapy. And some evidences have showed these: carcinomas arising from serrated pathway tends to have lesser 5-year survival but again the causes of this comportment are not available, and the answer may be found as the genetic alterations becomes evident [47].

For now, it is clear that serrated pathway is a well-established pattern that explains the behavior of some hyperplastic and serrated polyps that could not have been explained in the classical adenoma-carcinoma sequence using CIN and MSI models. Even with lacks in knowledge for profound understanding, the pathological and molecular characterization of these polyps are constantly progressing and studies in the next few years will probably show the best way to manage these cases in clinical practice [47].

3. Conclusion

There have been significant advances about tumor molecular biology, will allow us to apply this knowledge in more specific diagnostic techniques, a proper diagnosis, with the possibility of detecting earlier pre-malignant lesions and diagnoses. This applied research knowledge would allow the development of more efficient therapies for cancer, moreover, it can act in prevention.

The application of molecular biology knowledge in the diagnosis and treatment of colorectal cancer generates a great impact on the accuracy of diagnosis and optimization of cancer therapy in order to individualize the treatment, thereby trying to reduce the uncertainty about the effectiveness of the treatment that will be accomplished.

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