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Review

The role of TP53, APC, and KRAS gene polymorphisms in the development of colorectal cancer

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Summary

This paper discusses about colorectal cancer in correlation with certain genes. Based on the etiological factors, colorectal cancer can be stratified into familial, hereditary, and sporadic. Explorations into hereditary syndromes such as familial adenomatous polyposis and hereditary non-polyposis colorectal carcinoma have unveiled genomic alterations in APC, KRAS, and TP53 genes, which are also implicated in the pathogenesis of sporadic carcinoma.

Colorectal cancer constitutes a malignant epithelial neoplasm and ranks among the most prevalent malignancies afflicting both sexes. Despite a persistently elevated mortality rate, the incidence of this carcinoma has exhibited a declining trend over the past decade, though it still represents a substantial public health concern.

Advancements in research methodologies have led to the identification of rarer syndromes and their associated genes. Investigation of APC, KRAS, and TP53 genes contributory to the genesis of rare syndromes, in conjunction with previously documented genetic instances, has unveiled the mechanistic underpinnings of carcinogenesis. This has facilitated the development of more precise therapeutic modalities.

Despite the notable plethora of newly discovered genetic alterations across various genes, it is imperative to persist in research endeavors to comprehensively elucidate the nature and significance of colorectal carcinoma development processes.

Key words: colorectal carcinoma, TP53, KRAS, hereditary syndromes, carcinogenesis

Introduction

The morbidity and mortality rates are severely impacted by colorectal cancer (CRC), which is a huge socio-epidemiological problem worldwide. The International Agency for Research on Cancer (GLOBOCAN) reports that the prevalence of CRC in the world's population is the third among males (746,000 cases, or 10.0% of all cases), and the second among females (614,000 cases, or 9.2% of all cases) [1]. It is also one of the most prevalent and deadly cancers, killing 835,000 people annually

and afflicting 1.65 million people annually [2]. In Republic of Srpska, CRC ranks the second among all types of cancer, with a prevalence of 12.3% among men and 10.4% among women in the year 2014 [3].

Therefore, it is crucial to comprehend the mechanisms and genes responsible for its development. Insights into the alterations leading to the onset of CRC may lead to improvements in its diagnosis and treatment. At the transition from the small intestine, we encounter the cecum, followed by the ascending colon, often referred to as the right colon. Anatomically, the colon comprises several segments that continue from the small intestine (ileum). Colorectal cancer most commonly originates in the right colon or the proximal left colon before spreading to encompass the entire region. The extent of involvement varies concerning the set of mutated genes and the precursor syndromes such as Lynch syndrome (hereditary nonpolyposis colorectal cancer, HNPCC) and familial adenomatous polyposis (FAP). The transverse colon resides between the right and left colon, followed by the descending colon, and subsequently, the sigmoid colon, culminating in the rectum and anus [4].

Ninety percent of all colorectal tumors are adenocarcinomas, while the remaining 10% commonly consist of lymphomas, carcinoids, or sarcomas. In addition to historical and clinical indicators that can raise suspicion of CRC diagnosis, the diagnosis is aided by the detection of soluble oncogenic biomarkers such as carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) [5, 6]. However, a colonoscopy is absolutely necessary for correctly diagnosing CRC. If a colonic lesion is suspected, a pathology examination must be performed to confirm it. Radiological techniques are used in conjunction with tumour staging to decide the type of surgery, radiation treatment, and chemotherapy that should be used for CRC [7]. The TNM classification, which classifies malignant solid tumours, can be used to classify CRC. The size of the tumor, the number of afflicted lymph nodes, and the presence of distant metastases were taken into consideration by the American Joint Cancer Committee (AJCC) when dividing CRC patients into four stages [8]. Chemotherapy and surgical excision are currently the mainstays of CRC treatment. Chemotherapy may, however, not be effective, particularly in patients with advanced illness. Attempts at immunotherapy for CRC have also not shown to be very successful. After the therapy is used, many patients have months or even years of clinical illness remission. However, 30–50% of patients experience a disease return following a period of remission, most frequently in the form of distant metastases [9]. The reason for the death of these patients is the growth, spread, and metastasis of the primary tumor [9, 10].

During routine colonoscopy examinations, small benign tumors, known as adenomas, in the form of epithelial protrusions or polyps are frequently identified. It is believed that these adenomatous polyps serve as precursors to the majority of CRC [11]. In a significant number of cases, the carcinogenic process begins with an adenoma, eventually progressing to carcinoma. Polyps smaller than 1 cm in diameter predominantly contain non-tumor cells, while larger polyps often harbor abnormal, undifferentiated malignant cells. Throughout this protracted process, spanning several years, changes in the expression of multiple oncogenes and tumor suppressor genes are observed. The appearance of adenomas and subsequently malignant cells within the tissue results from the accumulation of a series of genetic changes, i.e., mutations, leading to disturbances in the control of epithelial cell growth and proliferation. Through the investigation of hereditary CRC, specifically the syndromes preceding it, genes such as TP53, KRAS, APC, and MMR genes have been identified to play roles in the development of sporadic CRC as well [11].

Etiology of colorectal carcinoma

Risk factors for the development of CRC can be categorized into non-modifiable and modifiable factors. Non-modifiable factors include age over 50 years and a positive family history of polyposis and inflammatory colon diseases. It is estimated that in 70% of cases, CRC is not inherited. However, data shows that it is inherited in 20% of cases, making a positive family history of CRC, FAP, and Lynch syndrome significant risk factors. The remaining 10% is attributed to de novo gene mutations that can lead to the development of CRC. Based on these risk factors, CRC is classified into three types: 1. sporadic, 2. familial, and 3. hereditary [12, 13]. While numerous external factors such as radiation, medications, and viral infections may contribute to tumorigenesis, the most influential factor in the development of CRC is a diet. Apart from diets rich in saturated fats, red meat, and a lack of dietary fiber, the causative agents of CRC also encompass genetic changes accrued over one's lifetime [14]. Colorectal cancer predominantly manifests in older individuals, and it is now believed that sustained exposure to various carcinogens over an extended period is required for tumor induction [15].

These data highlight the significance of genetics in the development of CRC. Modifiable risk factors that can be prevented include: unhealthy diet, obesity, diabetes, physical inactivity, alcohol consumption, and smoking [16, 17]. The significant geographic variations in the occurrence of CRC underscore the importance of diet as a crucial risk factor. The results of 13 cohort studies have demonstrated that the risk of CRC increases by approximately 18% when dietary fiber intake is reduced from 10–15 grams per day to below 10 grams daily [18, 19]. However, it has been demonstrated that CRC typically arises as a combination of these factors, most commonly sporadically, as a result of the accumulation of genetic changes in conjunction with various external influences identified as risk factors [20, 21].

Based on the causative factors we can distinguish three types of CRC:

- Familial CRC: This category includes individuals with relatives affected by CRC, but there is no evidence of inheritable characteristics [22]. The occurrence of familial CRC is largely attributed to environmental factors. Consequently, affected members of the same family exhibit mutations in different genes or are genetically unrelated;
- Sporadic CRC: Defined as CRC occurring in individuals with no recorded similar cases in their families [22]. In other words, sporadic CRC arises from the spontaneous accumulation of critical mutations in specific genes;
- Hereditary CRC: This term describes cases where autosomal dominant inheritance of a gene associated with tumor development is evident within a specific family [22]. This category encompasses individuals with syndromes preceding the onset of colorectal cancer. The most well-studied syndromes in this context are FAP and Lynch syndrome. The analysis of these syndromes has led to the discovery of some of the most important genes responsible for CRC development (Table 1). Mutations in these genes have also been identified in a significant number of sporadic CRC cases [11].

According to this hypothesis, the tumorigenesis necessitates the loss of both alleles of a specific tumor suppressor gene. One mutation may be inherited, and in such cases, the heterozygous gene remains active, producing the correct protein. To explain the onset of CRC, the Knudson two-hit hypothesis is crucial. This mutation is carried by all cells in the body, and the type of potential tumor depends solely on the position of the cell where the second mutation occurs. If a person does not have an inherited mutation, two hits are

required for tumorigenesis. For the potential development of a tumor, a specific tumor suppressor gene in certain cells must mutate in both alleles. This precisely elucidates the onset of sporadic CRC, and the same hypothesis applies to the other two types [11].

Table 1. Some of the genes involved in the development of colorectal cancer [11]

GENE	CLASS	ROLE	FREQUENCY IN CRC(%)
KRAS	Oncogene	Receptor tyrosine kinase signaling pathway	40
CTNNB1	Oncogene	WNT signaling pathway	5–10
TP53	Tumor suppressor	Stress/damage response	60
APC	Tumor suppressor	WNT signaling pathway	> 60
SMAD4	Tumor suppressor	TGF-β signaling pathway	30
Receptor TGF-β II	Tumor suppressor	TGF-β signaling pathway	10
MMR Genes	Tumor suppressor	Mismatch repair in DNA	15

Familial Adenomatous Polyposis

Adenomatous polyps predominantly emerge in the left colon within the first 10 years of life and can later spread throughout the colon [22]. Familial adenomatous polyposis (FAP) is an autosomal dominant hereditary disorder linked to the development of colorectal cancer. Its primary hallmark is the occurrence of numerous polyps along the entire inner surface of the colon, significantly elevating the risk of cancer development [23]. If FAP is not detected and treated in its early stages, there is an almost 100% risk of developing colorectal cancer by the age of 40, with cancer typically manifesting approximately 10 years after the onset of polyps. FAP is inherited through an autosomal mutation in the APC gene (Adenomatous polyposis coli), which is located on the fifth chromosome [24]. Changes in this gene, as well as a series of others, are associated with chromosomal aberrations such as numerous deletions, translocations, and aneuploidy. These mutations result in an atypical karyotype, often referred to as chromosomal instability (CIN) [11, 25]. While most patients have a family history of the disease, in approximately 25% of cases, mutations arise de novo [24]. Although this syndrome accounts for only 1% of all cases of CRC, alterations in the APC gene have been identified in over 85% of sporadic cases [26].

Hereditary Nonpolyposis Colorectal Cancer

Hereditary Nonpolyposis Colorectal Cancer (HNPCC), also known as Lynch syndrome, is inherited in an autosomal dominant manner and is the most common hereditary syndrome responsible for 5% of CRC cases [25]. In addition to hereditary syndromes caused by mutations in the APC gene, there is another, more prevalent syndrome that leads to the development of cancer in the right part of the colon. This syndrome, known as hereditary nonpolyposis colorectal cancer - HNPCC, increases the risk of developing CRC independently of the number of adenomatous polyps [11]. Besides elevating the risk of CRC, it is also associated with the occurrence of other forms of tumors such as ovarian, gastric, brain, skin, and more [24]. Recently, a connection has been established between HNPCC and the *EPCAM* gene, where mutations at the 3' end lead to the silencing of the MSH2 gene

[25]. It has been observed that HNPCC is associated with alterations in microsatellite regions, which are areas where short DNA motifs of 2 to 5 base pairs repeat. This phenomenon is known as microsatellite instability (MSI), and the alterations do not cause significant changes in the karyotype [27]. Subsequently, a similarity has been noted between the MSI phenotype and the yeast phenotype with altered DNA mismatch repair (MMR) genes. This resemblance leads to the identification of five MMR genes associated with HNPCC. The first ones discovered and the most prevalent are *MSH2* and *MLH1*, with mutations recorded in approximately 70% of HNPCC cases [26]. Alongside *MSH2* and *MLH1*, genes *PMS1*, *PMS2*, and *MSH6* were soon identified and described, all of which are also involved in carcinogenesis. Although HNPCC itself accounts for only 5% of CRC cases, mutations in genes responsible for its onset are linked to approximately 15% of sporadic CRC cases [25].

Correlation with other syndromes

Attenuated Familial Adenomatous Polyposis (AFAP)

AFAP (Attenuated Familial Adenomatous Polyposis) - Polyps, as in typical FAP, appear in the left colon, usually around the age of 40, while CRC develops approximately 10 years after the onset of polyps. The onset of this form of FAP is also associated with mutations in the *APC* gene, specifically mutations in its 5′ or 3′ region [28]. Attenuated adenomatous polyposis of the colon is a less aggressive variant of FAP, with lower polyp incidence in later life and a reduced risk of CRC [24].

Peutz-Jeghers Syndrome (PJS) Factors

PJS (Peutz-Jeghers Syndrome) is a very rare autosomal dominant disorder characterized by the presence of multiple polyps, even in the small intestine. This syndrome is associated with a high risk of developing CRC and, in women, breast cancer. The appearance of PJS is linked to a mutation in the tumor suppressor gene *STK-11* [24].

MUTYH-Associated Polyposis (MAP)

MAP (MUTYH-Associated Polyposis) often exhibits clinical features of FAP but is not associated with mutations in the APC gene, but rather with the *MUTYH* gene. Individuals with this syndrome have an 80% risk of developing CRC by the age of 40 [24].

Juvenile Polyposis Syndrome (JPS)

JPS (Juvenile Polyposis Syndrome) - Although the name may suggest the appearance of symptoms in young individuals, they do not exclusively occur in youth. In this case, the term "juvenile" refers to the primitive structure of the connective tissue in the polyp [23].

Affected individuals are divided into three groups:

1. Individuals with small clusters of polyps;
2. Individuals with polyps throughout the entire colon;
3. Individuals with a family history of JPS.

The risk of malignant transformation of these polyps is 40%, and genes associated with the syndrome include *SMAD4*, *BMPR1A*, and *PTEN* [24].

Hyperplastic Polyposis (HPP)

HPP (Hyperplastic Polyposis) is an extremely rare syndrome characterized by the main symptom of developing multiple and large polyps in the colon. Individuals with this syndrome have a high likelihood of developing

CRC by the age of 50, although cases have been recorded at earlier ages. While there are rare familial cases of this syndrome, the inheritance pattern has not yet been definitively established. Certain cases show mutations in the *MUTYH* gene, but this association has not been fully confirmed [28].

Analysis and genes related to CRC developement

Regarding the origins of CRC, there are two theories. The "adenoma-carcinoma sequence," the first theory, contends that adenomatous polyps are the origin of 80% of all CRC. In the second hypothesis, CRC starts *de novo*. According to this theory, CRC is caused by the lack of tumor suppressor gene (TSG) activity and the activation of mutant oncogenes. According to some authos, CRC requires four to five mutations to manifest, and the overall number of genetic changes is far more crucial than the order of mutations [13, 29, 30]. Under normal circumstances, TSG control the growth of malignant cells by regulating cell division. Mutated forms of these genes lose their function, leading to uncontrolled cell proliferation [31]. Two types of genes responsible for regulating the cell cycle are involved in this process. Proto-oncogenes control cell growth and differentiation but, when mutated, bypass regulatory mechanisms and become highly active oncogenes. Fearon and Vogelstein proposed a genetic model in the 1990s (Figure 1) that explains the gradual formation of CRC. They outlined three important characteristics: CRC arises due to mutations in oncogenes and tumor suppressor genes, the formation of a malignant tumor requires at least four to five mutations in key genes and mutations often occur in a specific sequence, but the cumulative accumulation of changes is more important [29].

Genes like TP53 (tumor protein p53), *APC* (adenomatous polyposis coli), and KRAS (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) have been found to play a substantial role in the development of sporadic type CRC through the interpretation of hereditary CRC [32]. Normal circumstances involve the regulation of the cell cycle by tumor suppressor genes like *TP53* and *APC*, which prevent the formation of tumor cells by limiting cell division [13, 33]. A tumor suppressor gene called TP53 can be found at location 13.1 on the short arm of chromosome 17. It produces the p53 protein, which controls the cell cycle and can stimulate the production of genes involved in DNA repair or induce cell apoptosis [34, 35]. APC, which is placed on long arm of chromosome 5 at location 22.2, is a gene that codes for a protein that is present in post-mitotic epithelial cells. The cell cycle and cell proliferation are both regulated by the APC protein [36, 37]. The proto-oncogene KRAS is found on chromosome 17p12.1. It controls cell proliferation and differentiation under normal physiological circumstances [13, 33]. In figure 1 genetic changes responsible for the progression from normal epithelial cells to malignant are shown [38].

According to research, TP53, APC, and KRAS gene mutations are frequently found in CRC patients and can result in the malignant transformation of cells [13, 33–37, 39–42].

Researchers are becoming more interested in the effects of gene mutations, particularly hereditary (germline) changes that are a part of a person's genetic makeup, in addition to mutations affecting "cancer" genes within the target tissue and directly responsible for the process of malignant cell transformation. These inherited alterations, which also involve DNA polymorphisms, provide a favourable environment for the negative impacts of outside causes. Nucleotide diversity, also known as DNA polymorphisms, refers to changes in the inherited genetic code. Its definition is the ratio of the number of distinct bases to the total number of base pairs in the compared genomes [43–46]. Single nucleotide

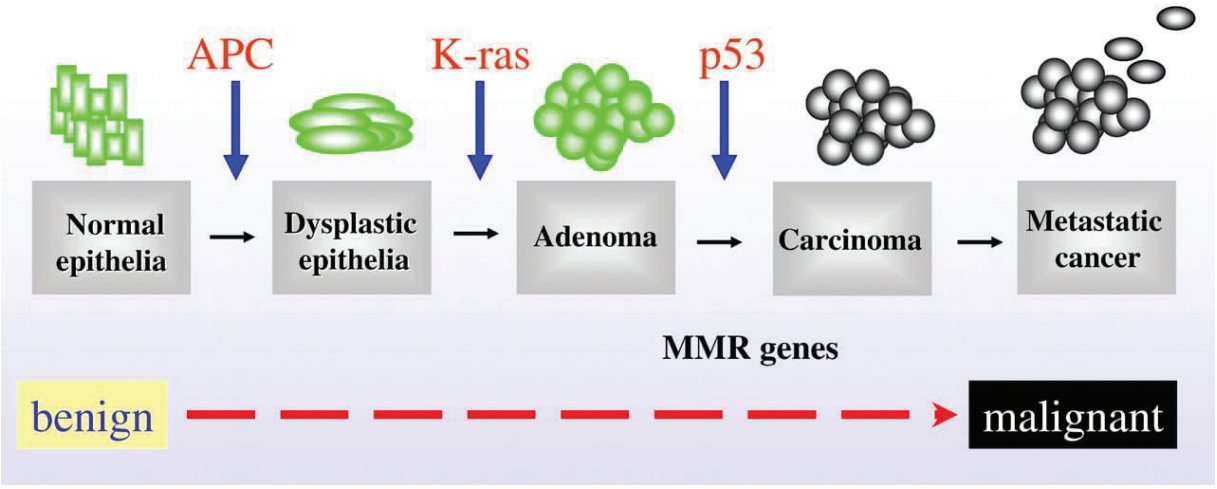

Figure 1. Genetic changes responsible for the progression from normal epithelial cells to malignant [38]

polymorphisms (SNPs) represent variations in the DNA sequence, meaning that at a specific location in the genome, one individual may have one nucleotide, while another individual may have a different nucleotide [47]. Understanding SNPs is important for better defining the pathophysiological mechanisms of multifactorial diseases, including malignancies [43, 44]. Investigating the relationship between SNPs and illnesses is the foundation of whole-genome association studies (GWAS). Many research teams have investigated SNPs as CRC susceptibility markers since the introduction of GWAS. Different groups of genes polymorphisms can considerably raise the risk of CRC. A review of previously published studies and available SNP databases has identified more than 500 polymorphisms in 110 different genes that are associated with CRC [48]. To date, particular focus has been placed on polymorphisms in genes that regulate the synthesis of inflammatory mediators and regulators, as well as enzymes involved in processes like DNA synthesis and methylation and other processes important to the transformation of neoplastic cells. The TP53, APC, and KRAS gene polymorphisms, known to be connected to the development of polyps into cancer, are, nevertheless, the subject of scant scientific study. Consistently, statistical significance has been demonstrated for 16 variations spanning 11 genes that govern this transition [48].

TP53

The cell cycle consists of several phases, with the main regulatory point (the so-called restriction point) occurring at the transition from G1 to S phase. The tumor suppressor gene TP53 encodes the protein p53, also known as the "guardian of the genome," which can activate the expression of genes related to DNA repair or cell apoptosis while regulating the cell cycle [22]. In addition to the classical factors for cell cycle control, the influence of the p53 protein is crucial at this control point. Elevated levels of p53 due to DNA damage lead to cell cycle arrest, and depending on the extent of damage, repair genes are activated, or apoptosis is signaled [49]. Mutations in the TP53 gene result in the loss of p53 protein function, which can lead to the replication of damaged DNA in the S phase. Although mutations only cause a change in a single amino acid of the p53 protein, this alteration can result in a misreading of information and, consequently, the

loss of function. Mutations in the TP53 gene are found in more than 50% of all tumors and are also present in a significant number of colorectal cancer cases [22]. Through this process, mutations accumulate, potentially leading to the development of cancerous cells.

Multiple studies have confirmed that the TP53 codon 72 polymorphism is associated with an increased risk for CRC [50, 51]. Single-nucleotide polymorphism rs1042522 has recently become a target for intensive research as it can affect both the risk of cancer development and the results of anticancer therapy [52]. The TP53 Arg72Pro mutation (Arg to Pro), results in three different genotypes: Arg/Arg, Arg/Pro, and Pro/Pro [53]. A protein produced as a result of these mutations demonstrates a reduced capacity to bind to a specific DNA sequence that regulates the p53 transcriptional pathway. This leads to the altered performance of the p53 protein in the induction of growth arrest and apoptosis [54].

The frequency of the TP53 Pro72Pro genotype was shown to be significantly (p=0.0033) higher in patients with CRC compared to the control group of healthy individuals in the study by Sungamseti et al. [55] thus representing a significant risk factor for the development of CRC. The TP53 Pro72Pro genotype was discovered to be a significant risk factor for the development of CRC (Pro72Pro; OR = 3.80, 95% CI = 2.46–5.88, 2 = 61.27, p=0.0001) in a molecular-genetic cohort analysis of CRC in Kazakhstan [56].

KRAS

This gene encodes the KRAS protein, which carries out self-inactivation by binding to GTP and converting it to GDP. The KRAS gene, located on chromosome 17p12.1, is one of the most frequently activated oncogenes. Changes in the sequence of this gene have been detected in 17–25% of all tumors, including approximately 50% of CRC cases. In normal conditions, external signals promote the accumulation of GTP, which binds to the signaling protein KRAS, thereby activating it. The protein becomes inactive through the hydrolysis of GTP into GDP, causing the signal transmission to cease [57].

Aside from changes in proliferation signaling, apoptosis, and metastasis, KRAS mutations are also associated with the development of an abnormal karyotype, namely chromosomal instability (CIN). KRAS remains constantly activated, disrupting cell cycle control. In CRC cells, the KRAS gene commonly accumulates point mutations in exons 12, 13, and 61, greatly reducing the GTPase activity of the protein. It is hypothesized that CIN occurs due to changes in the organization of the cytoskeleton during cell division, which is typically regulated by KRAS. In recent years, it has been observed that cells from patients with specific KRAS mutations are resistant to apoptosis induced by chemotherapy. Although this knowledge supports research that predicts low chances of curing patients with KRAS mutations, it also serves as a starting point for the discovery of new treatment methods [39]. Although KRAS gene mutations are found in 30% of CRC patients, they are uncommon in the general population and have a limited role as a biomarker for CRC risk. Because of this, several studies have concentrated on figuring out the KRAS gene's higher prevalence of polymorphisms. The 3'-UTR region of the KRAS gene has the polymorphism c.2505T > G (rs61764370), which has been thoroughly investigated for its relationship to CRC. But further research is required to properly comprehend the importance of Rajan and colleagues' findings, which showed a connection between rs61764370 and the likelihood of mortality in late-stage patients [58]. The findings are conflicting, and most studies claim that this polymorphism is not a substantial risk factor for the development of CRC [59, 60]. Smith et al. [61] did demonstrate the similar connection, but with

the survival of patients in the early stages of the disease. However, Liu et al. [62] showed that the rs8720 polymorphism, which is similarly found in the KRAS gene's 3'-UTR region, was strongly linked to the development of CRC, lower survival, and worse prognosis for the illness.

APC

Although most individuals with mutations in this gene develop colorectal cancer (CRC), the number of polyps and the age at which they occur are determined by the location of the mutation within the APC gene (NIH, n.d.). To date, over 700 mutations in the APC gene have been documented in individuals with familial adenomatous polyposis (FAP) syndrome, including various deletions, frame-shift mutations, and point mutations. The APC gene is located on the long arm of chromosome 5 at position 22.2 (5q22.2) and encodes a protein found in post-mitotic epithelial cells. Chromosomal abnormalities associated with mutations in this gene have been observed in the genomes of CRC cells, resulting in a phenotype known as chromosomal instability [27]. It is well-established that the APC protein plays a role in regulating the cell cycle, cell adhesion and migration, as well as chromosome segregation. One of its functions is binding to cytoskeletal elements, specifically microtubules, thereby contributing to the formation of the mitotic spindle [27]. When the APC gene is functional and there is no external WNT signal, the protein complex including APC binds to β-catenin and phosphorylates it, signaling for its degradation. However, in the presence of a WNT signal or in the case of a non-functional APC protein, β-catenin remains unphosphorylated and enters the nucleus where it activates the transcription of proliferation genes. Therefore, it is clear that APC plays a crucial role in the WNT/β-catenin signaling pathway that regulates cell proliferation. In this context, transcription factors in the nucleus retain their function and position, leading to the transcription of genes. In normal cells, this process is controlled by external WNT signaling glycoproteins. However, when the APC gene mutates, there is constitutive expression of these genes in cells. In addition to APC mutations, in a small number of cases where this mutation is not detected, mutations in the CTNNB1, AXIN1, and AXIN2 genes have been identified, which also encode proteins involved in this signaling pathway [27]. In the study of Segditsas et al. [63] it is stated that FAP is caused by mutations in the APC gene. FAP, however, only makes up a minor portion of CRC cases. Researchers started looking into whether a higher prevalence of APC gene polymorphisms indicated a risk for the development of CRC which etiopathogenesis was not explained by mutations because of the documented relationship between FAP and CRC (39). The three most thoroughly investigated APC gene polymorphisms for this purpose were c.3920T>A (p.Ile1307Lys; rs1801155), c.3949G>C (p.Glu1317Gln; rs1801166), and c.5465T>A (p.Val1822Asp; rs459552), according to a meta-analytical study by Liang et al [64]. Despite rs459552 being the most prevalent APC variant, the scientists found that all three polymorphisms were strongly linked to the onset of CRC [64, 65].

Conclusion

Colorectal cancer (CRC) represents a significant global health challenge, characterized by its complex etiology encompassing sporadic, familial, and hereditary forms. This review comprehensively highlights the indispensable roles of the TP53, APC, and KRAS genes and their respective polymorphisms in CRC carcinogenesis. We have demonstrated how germline and somatic mutations in these genes drive the initiation and progression of both

sporadic CRC and various hereditary polyposis and non-polyposis syndromes, including Familial Adenomatous Polyposis (FAP) and Lynch syndrome.

Understanding the intricate molecular pathways governed by TP53, APC, and KRAS mutations is paramount for deciphering CRC pathogenesis. This knowledge not only enhances our ability to stratify patient risk and improve diagnostic accuracy, but also paves the way for the development of more precise, targeted therapeutic strategies. While considerable progress has been made in identifying the genetic landscape of CRC, continuous research into the interplay of these and other genetic factors remains crucial. Such efforts will ultimately contribute to personalized medicine approaches, leading to improved prevention, early detection, and more effective management of colorectal cancer.

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Uloga TP53, APC i KRAS genskih polimorfizama u nastanku kolorektalnog karcinoma

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U ovom radu govorimo o kolorektalnom karcinomu u korelaciji sa određenim genima. Prema uzroku nastanka, kolorektalni karcinom možemo podijeliti na porodični, nasljedni i sporadični oblik. Istraživanjem nasljednih sindroma poput porodične adenomatozne polipoze i nasljednog nepolipoznog kolorektalnog karcinoma otkrivene su promjene gena APC, KRAS i TP53 uključenih u razvoj sporadičnog karcinoma.

Karcinom debelog crijeva je maligni epitelni tumor i jedan od najčešćih oblika malignih promjena koje zahvataju oba pola. Uprkos još uvijek visokoj stopi mortaliteta, posljednjih desetak godina učestalost ovog karcinoma se smanjuje, ali još uvijek predstavlja veliki zdravstveni problem.

Razvojem metoda istraživanja otkriveni su i neki manje učestali sindromi te geni koji se s njima povezuju. Istraživanjem gena APC, KRAS i TP53 koji učestvuju u nastanku rijetkih sindroma i ranije otkrivenih primjera drugih gena otkriveni su mehanizmi karcinogeneze što je omogućilo razvoj preciznijih metoda liječenja.

Uprkos značajnom broju novootkrivenih promjena u različitim genima potrebno je nastaviti istraživanja da bi se u potpunosti razumjeli priroda i značaj procesa razvoja karcinoma debelog crijeva.

Ključne riječi: kolorektalni karcinom, TP53, KRAS, nasljedni sindromi, kancerogeneza